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FOLLICULITIS ULERYTHEMATOSA RETICULATA

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IN 1918 one of us (G. M. M.) and Parounagian published an article entitled "Folliculitis Ulerythematosa Reticulata" in which several statements subsequently were found to be misleading or erroneous. Priority for the first case of this disease was credited to Whitehouse (1913). Credit was given Pernet for publishing the first clinical description and the first clinical photograph in a bona fide case (1916). Darier, in 1920, and others, later, called attention to Thibierge's recognition of the disease as an entity and his publication of a short clinical account under the legend acné vermoulante, in Brocq's "La pratique dermatologique," in 1900. MacKee and Parounagian were familiar with this report, but failed to identify the case as one of folliculitis ulerythematosa reticulata. We now declare the case to be a bona fide example of the disease. Also, as it is the first published report that we have been able to find, priority should be given Thibierge. Pernet appears to have been the first to publish a clinical photograph of the manifestations of the disease.

As stated in their article, MacKee and Parounagian were familiar with Unna's description of a disease which he called ulerythema acneiforme (1894). They did not identify Unna's case as one of folliculitis ulerythema reticulata. They had overlooked Unna's illustrations which accompanied a previous report published in the "International Atlas of Rare Skin Diseases" (1889). Attention was called to this omission by Corson and Knowles (1924). We have examined these illustrations, which are both clinical and histologic. We believe that Unna's case is not one of folliculitis ulerythematosa reticulata. It appears to resemble what has been described as nevus follicularis keratosis, nevus acneiformis or nevus unilateralis comedonicus. We think, also, that the case described by Corson and Knowles belongs in this group.

MacKee and Parounagian were the first to study and describe the histology of folliculitis ulerythematosa reticulata. We have failed to find

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any disagreement with their histologic interpretation nor any important additions.

They called attention to clinical comedos, and so have other authors. The follicular lesion is a keratotic plug (follicular hyperkeratosis) rather than a true comedo.

The article of 1918 called attention to erythema. Some authors have stated that erythema is present, while others have declared the opposite. When viewed from a distance, the cheeks of some patients seem to be diffusely flushed. On close inspection, in many cases, the ridges are the color of normal skin or even a trifle paler, whereas the depressions are redder than the normal skin. This is not caused by inflammation but by the thin epidermis. In some instances there may be some secondary inflammation, such as reported by Barber.

There has been general agreement that the nosologic position of the disease is in the congenital keratosis group (nevoid), as stated in the article of 1918. With the aforementioned exceptions, the clinical description of the disease as given in the article was correct and need not be repeated here.

The disease has been given different names by various authors: acné vermoulante (Thibierge), atrophodermia reticulata (Pernet), folliculitis ulerythematosa reticulata (MacKee and Parounagian), folliculitis atrophicans reticulata (Little), atrophodermia vermiculatée (Darier) and vernacular terms, such as reticulated atrophy, honeycomb atrophy and worm-eaten atrophy. All authors agree that therapeutic methods thus far employed are useless. The consensus is that after reaching maximum development the eruption tends to improve spontaneously and may almost disappear after many years.

SUBSEQUENT HISTORY IN CASES PUBLISHED IN 1918

Case 1.—L. F., a boy aged 9 (case 2, 1918 article), remained under observation for about a year. He received ultraviolet rays in frequent erythema doses with an air-cooled quartz-mercury vapor lamp and in a number of blistering doses with a Kromayer lamp under pressure sufficient to dehematize the skin. He also received twelve treatments with unfiltered roentgen rays at weekly intervals, each of which consisted of 75 r at 100 kilovolts. At another time desquamating lotions and ointments were prescribed. At the end of the period of observation there was slight improvement.

Case 2.—G. B., a girl aged 16 (case 1, 1918 article), like L. F., remained under observation for about a year, during which time she received the same treatment except that the total dose of roentgen rays was considerably larger. At the end of the period of observation there was little if any improvement.

Eleven years later she again came under observation, on Dec. 9, 1929, at the age of 30. There had been considerable improvement. Either the ridges had flattened or the intervening spaces were less depressed, because the reticulated appearance had become much less conspicuous and the depressions had become paler (fig. 1). There were no visible horny follicular plugs, but there were several

milia. No new areas were involved, and the contour and location were unchanged. She was in good general health. She had married and had three healthy normal children, the oldest of which was 10.

There was slight atrophy of the skin of the cheeks and anterior surface of the neck. In the latter location were moderate telangiectasia and pigmentary changes.

On the left side of the face, near the outer end of the eyebrow, there was a clinical basal cell epithelioma about 1 cm. in diameter. There was a smaller similar

Fig. 1 (G. B., case 1 of 1918 article).—*A*, eleven years after original course of treatment. The original cribriform pattern is barely noticeable. There is chronic radiodermatitis of the front aspect of the neck, a basal cell epithelioma in the center of the cheek and a basal cell epithelioma on the nose. *B*, slight reticulation of the cheek is still present. There is a basal cell epithelioma on the forehead and chronic radiodermatitis of the anterior part of the neck.

lesion on the right side of the nose and another in the center of the right cheek. These lesions were excised. The histologic structure was that of basal cell epithelioma and chronic radiodermatitis. In addition, there were several small keratoses scattered over the face. These were destroyed with electrocoagulation and curettage under local procaine hydrochloride anesthesia. All wounds healed normally. The patient remained under observation for one year, during which time there was no recurrence and no new lesions developed. She has not been seen since 1930.

Comment.—It is probable that improvement in these patients (L. F. and G. B.) was spontaneous. The pigmentary changes, the telangiectasia and some of the atrophy were sequelae of treatment with roentgen rays. Basal cell epitheliomas in chronic radiodermatitis are not uncommon, but the consensus at present is that such lesions are not sequelae of radiodermatitis but that they would have developed anyway. As their location was beyond the area occupied by the original eruption, they cannot be called sequelae of folliculitis ulerythematosa reticulata.

REPORT OF NEW CASES

CASE 1.—H. S. was a healthy Jewish boy of 16 years (fig. 2). His younger brother (U. S., case 2) had the same disease in the same location (both cheeks). Otherwise, the family history was irrelevant. The duration was uncertain. The disease was thought to have begun at the age of 8. The clinical description given in case 1 in the article of 1918 fits this patient almost exactly. The distribution was the same except that in H. S. there was slight involvement of the left upper eyelid, close to the eyebrow, and an upward extension on the left cheek, between the ear and eye to about the level of the eyebrow. There were the same tiny depressions, a little redder than the normal skin, separated by the same ridges and giving rise to the same reticulation. There were fewer milia and horny plugs. There had been no treatment. A biopsy was not permitted.

CASE 2.—U. S. (fig. 3) was a healthy Jewish boy, aged 13 and a brother of H. S. (case 1). The eruption on his face was said to have begun at the age of 11. The eruption, in almost every detail, was the same as that of his brother, except that it was less conspicuous. Permission for a biopsy was refused.

Comment.—These 2 patients (H. S. and U. S.), brothers, presented typical although mild examples of the disease. Bruck reported 2 typical cases in brothers. Barber reported the cases of a brother and sister who had folliculitis decalvans and lichen spinulosus in addition to folliculitis ulerythematosa reticulata. Under the title *acné vermoulante,* Péna published the cases of twins who had a "worm-eaten" eruption of the cheeks. Many aspects of the eruption differed from the characteristics of folliculitis ulerythematosa reticulata. For instance, the grooves and depressions were much deeper, and there was no reticulation. We regard Péna's cases as representing a somewhat similar disease, but not true examples of folliculitis ulerythematosa reticulata. Scomazzoni reported 2 probable cases of folliculitis ulerythematosa reticulata in

sisters. Weiss reported 2 cases in sisters, but they were probably examples of Heidingsfeld's atrophia maculosa varioliformis rather than folliculitis ulerythematosa reticulata. Mendes da Costa published bona fide cases in mother and daughter. The daughter had other congenital anomalies, consisting of irregularly formed teeth, abnormal hair and a mongoloid appearance. Oppenheim reported a father and 6 sons who

Fig. 2 (H. S.).—*A*, showing the worm-eaten appearance of the right cheek, and *B*, showing the cribriform pattern resembling a telescopic view of the moon at first quarter.

had atrophodermia vermiculata and ichthyosis follicularis. Carol, Godfried, Prakken and Prick reported a family in which several members suffered from congenital defects—von Recklinghausen's disease, heart block, mental deficiency and other anomalies. Three members had

probable folliculitis ulerythematosa reticulata of the cheeks. In 1 of these, a girl of 19, the neck and extremities were involved. The clinical photograph of the face of this girl does not suggest the disease. There seems to be a large number of papules (probably keratotic), but few if any minute depressions and no reticulation. The histologic study, however, does suggest folliculitis ulerythematosa reticulata. The photograph of the face of the girl's mother does suggest the disease, although the depressions are unusually large and there is not a conspicuous cribriform pattern.

It is interesting to note that the disease may be familial and that it may be accompanied with other congenital anomalies.

Case 3.—G. H. was a Jewish boy 9 years of age (fig. 4). The family history was irrelevant. The disease began at the age of 7. He was seen by us once only,

Fig. 3 (U. S., brother of H. S.).—A mild example of the disease.

on Nov. 11, 1930. The eruption occupied the greater part of each cheek, and it was approximately symmetric. There were a few lesions on each side of the forehead and each side of the chin. Scattered throughout the affected areas was a moderate number of comedos or follicular keratotic plugs. Milia, papules and oily seborrhea were not present. There were numerous small, linear, oval and irregularly shaped areas of atrophy and tiny shallow pits. The areas of atrophy were both confluent and discrete, but the reticulation and cribriform pattern so characteristic of folliculitis ulerythematosa reticulata were absent except in a few small areas where the pits were confluent. The oval and irregular areas of atrophy were shallow and slightly redder than the normal skin, and they ranged in diameter from 0.25 mm. to 2 mm. In the larger areas there were tiny projections of apparently normal skin, which produced a nutmeg grater sensation on delicate palpation. The linear areas were 1 mm. or less in width. In length they ranged from 2 or 3 mm. to 2 cm. They were shallow, smooth and paler than the normal skin. Most of them

extended downward and outward. The skin between the linear depressions was normal. A biopsy was refused.

Comment.—We are unable to make an unequivocal diagnosis in this case. It has some, but lacks many, of the clinical features of folliculitis ulerythematosa reticulata. Location, distribution, symmetry, keratotic follicular plugs, age and atrophy are in favor of that diagnosis. Lacking are the fairly regular depressions and ridges—cribriform arrangement. Linear areas of atrophy are not characteristic of the disease. It does not resemble the grouped comedos of infants and children, nevus acneiformis, nevus comedonicus unilateralis, Heidingsfeld's atrophia maculosa varioli-

Fig. 4 (G. H.).—A case of probable mild folliculitis ulerythematosa reticulata, showing the long narrow areas of atrophy.

formis cutis, Unna's ulerythema acneiforme, White's nevus follicularis keratosis or any other disease with which we are familiar. We present the case as a probable mild aberrant example of folliculitis ulerythematosa reticulata.

REVIEW OF LITERATURE

We have examined over seventy articles and reports of cases in an effort to determine the number of bona fide cases of folliculitis ulerythematosa reticulata. The bibliography includes all these references. As shown in the accompanying table, we identified 28 such cases published by twenty-four authors. Because of inadequate clinical descriptions, no

histologic report, no clinical or histologic illustration or poor ones, a misleading title or our faulty interpretation of presented evidence, some genuine cases may have been missed. This is especially true of patients presented before dermatologic societies.

Possible and Probable Cases.—The subjoined authors have published cases some of which may be and some of which probably are examples of folliculitis ulerythematosa reticulata, but for reasons previously mentioned we are unable to identify them as such. The references and titles are in the bibliography: Carol, Godfried, Prakken and Prick, Heymann,

Chronologic List of Reported Cases

Author(s)	Date	Number of Cases	Term Used in Original Presentation
Thibierge	1900	1	Acné vermoulante
Whitehouse	1913	1	(Presented for diagnosis)
Pernet	1916	1	Atrophodermia reticulata symmetrica faciei
MacKee and Parounagian	1918	2	Folliculitis ulerythematosa reticulata
Little	1919	1	Folliculitis atrophicans reticulata
Darier	1920	1	Atrophodermie vermiculée
Pautrier	1922	1	Atrophodermie vermiculée
Fordyce and Abramowitz	1923	1	Folliculitis ulerythema reticulata
Spillmann	1923	1	Atrophodermie vermiculée
Casselberry	1923	1	Folliculitis ulerythematosa reticulata
Mendes da Costa	1926	2	Atrophodermia reticulata
Barber	1927	2	Folliculitis ulerythematosa reticulata
Vigne	1929	1	Atrophodermie vermiculée
Bruck	1930	2	Atrophoderma vermiculatum
Zoon	1930	1	Atrophodermia vermicularis
Oppenheim	1932	1	Atrophodermia vermiculata
Burgess	1932	1	Folliculitis ulerythematosa reticulata
Wertheimer	1932	1	Folliculitis ulerythematosa reticulata
Goldberg	1936	1	Atrophodermia vermiculata
Groneberg	1940	1	Atrophodermia vermiculata
Savatard	1943	2	Folliculitis ulerythematosa reticulata (honeycomb atrophy)
MacKee and Cipollaro	1947	2	Folliculitis ulerythematosa reticulata

de Amicis, Glingani, Kauczyński, Scomazzoni, Konrad, van Voornveld-Graciunescu, Etienne, Drouet and Louyot, Leven, Fülöp, Photinos and Nikas, Oppenheim (1929), Ostrowski, Haxthausen, MacKee and Cipollaro (1947 case 3), Brünauer and Sibley.

Rejections.—The following authors have presented cases which in our opinion do not represent folliculitis ulerythematosa reticulata, but belong in a group comprising diseases such as nevus comedonicus and nevus acneiformis. References and titles are in the bibliography: Parounagian, Unna, Heidingsfeld, Perry, Samuel, Dore, Weiss, Bechet, Gougerot and Burnier, Tanaka, Klepper, Pillsbury, Wallhauser, Péna, Corson and Knowles, Gans, Rasch and Oliver.

SUMMARY

The article of 1918 by one of us (G. M. M.) and Parounagian is reviewed and corrected. The condition of 1 of their patients eleven years after the original course of treatment is described. Two new cases and 1 probable case of the disease are added.

Thibierge is credited as having been the first to publish a case of a disease called folliculitis ulerythematosa reticulata and by a number of synonyms. Pernet is credited with publishing the first clinical photograph of the manifestations of the disease, and one of us (G. M. M.) and Parounagian are credited with having given the first histologic description. Whitehouse presented the first case in this country.

The literature is reviewed and a bibliography is appended. Synonymous titles are given, but no decision is made as to which name should be accepted. The nosologic position is in the group of congenital keratodermic anomalies. The disease is occasionally familial. It is at times accompanied with other congenital anomalies.

Twenty-eight genuine cases reported by twenty-four authors are identified. A chronologic table is included.

The disease is uncommon rather than rare. It is an easily recognized entity, but there may be borderline cases difficult to identify. The clinical and histologic descriptions in the article of 1918 remain essentially unchanged.

As yet, there is no satisfactory treatment. There is a tendency toward spontaneous improvement. The disease is of only esthetic importance.

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RECURRENT LUPUS VULGARIS FOLLOWING SURGICAL EXCISION AND REPLACEMENT SKIN GRAFT

Report of a Case with Evaluation of Surgical Treatment

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LUPUS vulgaris is relatively rare in the United States. In Europe the disease is common, and "lupus institutes" have been established in Denmark, Germany and Austria. In these institutes lupus vulgaris is treated conservatively with phototherapy (Finsen light), and considerable success has been reported with this treatment.[1] The cure of lupus vulgaris with phototherapy, however, requires months or years of treatment and special expensive efficient apparatus. Phototherapy is not a practicable treatment for lupus vulgaris in the United States because of the expense involved and the requirement of special hospital facilities. These adverse requirements of phototherapy have encouraged investigators in both Europe and the United States to seek a more rapid and less costly type of local treatment. Among the local types of treatment employed for lupus vulgaris are caustic chemicals,[2] scarification,[3] refrigeration,[4] electrocoagulation,[5] steam,[6] corn starch injections [7]

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4. Pusey, W. A.: The Use of Carbon Dioxid Snow in the Treatment of Nevi and Other Skin Lesions, J. A. M. A. **49**:1354 (Oct. 19) 1907.

5. Nagelschmidt, F.: Zur Diagnose und Therapie tuberkulöser Haut- affektionen, Deutsche med. Wchnschr. **33**:1631, 1907.

6. Hollaender, H.: Zur Immunpathologie und Therapie der Tuberkulose, Ztschr. f. Tuberk. **35**:81, 1921.

7. Kile, R. L.: Treatment of Lupus Vulgaris by Injections of Starch U.S.P. (Corn Starch): Report of Case, Arch. Dermat. & Syph. **39**:471 (March) 1939.

and surgical excision followed by a replacement skin graft.[8] Because in 75 to 80 per cent of cases lupus vulgaris is located on the face, the ideal type of local treatment sought by investigators has been one to yield the best cosmetic result. Of all local methods employed during the past fifty years, plastic surgical treatment has promised the best cosmetic result with the least treatment time and expense involved. Since 1890, numerous reports of cases of plastic surgical treatment for lupus vulgaris have appeared in the medical literature,[9] especially in Germany and France. The relatively few cases of lupus vulgaris encountered by physicians in the United States, on the other hand, have afforded American dermatologists little opportunity to treat the disease with surgical measures. The reports that have appeared in the United States,[10] however, are of great interest when compared with reports by European investigators. Whereas European dermatologists are almost unanimous in recording continuous excellent results from plastic surgical treatment for lupus vulgaris, most American dermatologists, employing similar surgical technic, have experienced frequent postoperative recurrence of lupus nodules in the skin graft or scar. A state of confusion thus exists at present in the United States as to the value of surgical excision and plastic repair in the treatment of lupus vulgaris.

An opportunity was recently afforded us to treat a patient with facial lupus vulgaris with the plastic surgical method. The postoperative recurrence of the disease in the skin graft and scar, in spite of wide and deep surgical excision of the lupus patch, encouraged us to make a survey of large American dermatologic clinics relative to their experience with this type of treatment. The answers received to our

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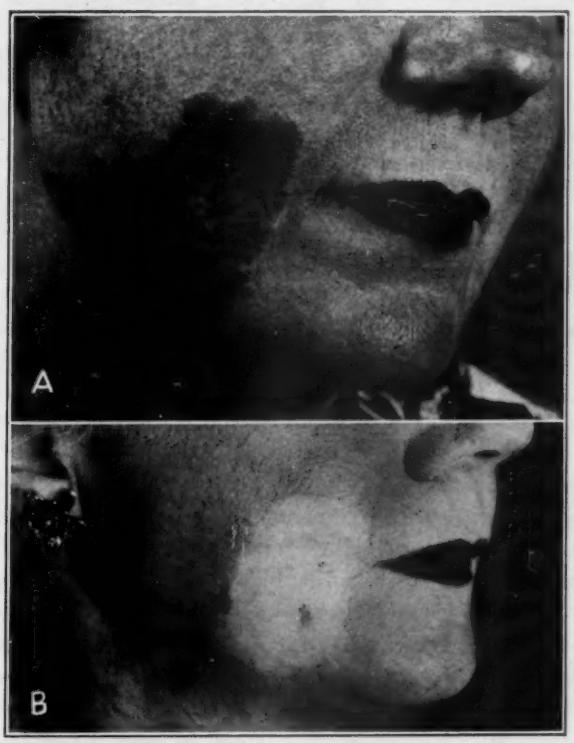
8. (*a*) Lang, E.: Der Lupus und dessen operative Behandlung, Vienna, J. Šafář, 1898. (*b*) Lang, E.: Die chirurgische Behandlung des Lupus, Deutsche med. Wchnschr. **36**:1161, 1910. (*c*) Lang, E., and Nélaton, M.: Sur les resultats de l'extirpation du lupus avec presentation des malades operes et gueris, Cong. internat. de dermat. et de syph. 1900, pp. 160-165.

9. Volk, R.: Tuberkulose der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankeiten, Berlin, Julius Springer, 1931, vol. 10, pp. 557-564.

10. (*a*) Van Rhee, G.: Lupus Vulgaris, Arch. Dermat. & Syph. **17**:574 (April) 1928. (*b*) Traub, E. C., and Kice, L.: Lupus Vulgaris, ibid. **29**:790 (May) 1934. (*c*) Brock, W. G.: Lupus Vulgaris of the Neck, ibid. **37**:367 (Feb.) 1938. (*d*) Hollander, L., and Shelton, J. M.: Replacement Grafts in Surgical Treatment of Lupus Vulgaris, ibid. **40**:263 (Aug.) 1939. (*e*) O'Leary, P.: Lupus Vulgaris, ibid. **41**:744 (April) 1940. (*f*) Traub, E. F.: Extensive Lupus Vulgaris Treated by Surgical Methods, ibid. **42**:1152 (Dec.) 1940. (*g*) Maliniac, J. W.: Surgical Treatment of Lupus of the Skin, Am. J. Surg. **55**:123, 1942. (*h*) Hollander, L., and Shelton, J. M.: Replacement Graft in Surgical Treatment of Lupus Vulgaris, Arch. Dermat. & Syph. **49**:60 (Jan.) 1944. (*i*) Montgomery, R. M.: Lupus Vulgaris, ibid. **52**:192 (Sept.) 1945.

questionnaire were almost unanimously unfavorable to the employment of surgical treatment in lupus vulgaris. These replies to our questionnaire were also in disagreement with the many favorable reports from European dermatologic centers and with the advocation of this type of treatment by leading American dermatologic textbooks. It is the purpose in this article, therefore, to report a case of facial lupus vulgaris in which the treatment used was surgical excision followed by replacement skin graft and in which the disease recurred postoperatively, and to evaluate the present status of the surgical treatment of lupus vulgaris.



A, patch of lupus vulgaris on the right cheek before surgical excision and plastic repair. *B*, plastic repair skin graft one year postoperatively, showing recurrent lupus vulgaris nodules in the skin graft and scar with extension on the right margin to healthy skin.

REPORT OF A CASE

History.—Mrs. B. J., a 50 year old white woman, was first seen in November 1943, because of a lesion present on her right cheek since early childhood. The lesion first appeared over forty years ago as a "spot," which slowly enlarged. She was told by a physician that the disorder was a "birthmark," and no treatment was given. Recently there had been more rapid increase of size of the lesion, with extension on the periphery and clearing in the center. Her personal and family history was without evidence of tuberculosis.

Dermatologic Examination.—On the right cheek was a well defined round area of about 3 inches (7.5 cm.) in diameter, with a scarred atrophic whitish center and

an elevated red-brown soft border. Under diascopic pressure "apple-jelly" nodules were noted in the border.

Laboratory Examinations.—The Wassermann reaction of the blood was negative. The blood cell count and the urine were normal. The result of a tuberculin test was negative. Roentgenologic examination of the chest showed an old healed calcified area of pulmonary tuberculosis in the subclavicular area on the right side and calcified lymph glands at the hilus of the right lung. A histologic examination of a biopsy specimen showed typical tubercle formation in the middle and upper layers of the cutis. The histologic diagnosis was lupus vulgaris.

Treatment and Course.—In March 1944, under local anesthesia, the lesion on the cheek was excised widely and deeply, with a safe margin of healthy tissue. A free thick skin graft from the abdomen was sutured into the defect with silk marginal sutures. The wound healed readily, and the sutures and dressings were removed in two weeks. An excellent cosmetic result was obtained. The patient consulted us again in March 1945, because of the appearance of several small brown "spots" in the skin graft area and operative scar. She stated that the dark spots first appeared about six months after the excision and had slowly increased in size. The examination showed several small soft brown nodules in the central portion of the skin graft and on the right margin of the scar, encroaching on the healthy skin. Under diascopic pressure the pigmented areas showed "apple jelly" nodules. The histologic examination of a biopsy section taken from a scar nodule showed lupus vulgaris. The diagnosis was recurrent lupus vulgaris following surgical excision and replacement skin graft.

COMMENT

Lang of Vienna was one of the first advocates of the surgical treatment for lupus vulgaris. From 1890 to 1910, Lang,[8a, b] Lang and Nélaton [8c] and Spitzer and Jungmann [11] reported over 300 cases of lupus vulgaris in which treatment with surgical excision and skin grafting was successful. During the past twenty-five years, Moure,[12] in France, and Salomon,[13] in Germany, have been the leading European exponents of the surgical treatment method for lupus vulgaris. A personal communication from Dr. G. Riehl, physician in chief of the Lupus Hospital in Vienna, revealed that during the three years, 1944-1946, 269 patients with lupus vulgaris were treated with surgical excision and skin grafting, with relapses in only 15 to date (5.6 per

11. Spitzer, L., and Jungmann, A.: Ergebnisse von 240 operierten Lupusfallen nebst Bemerkungen zur modern Lupusbehandlung, Vienna, J. Šafář, 1905.

12. (*a*) Moure, P.: Surgical Treatment in Lupus Vulgaris, Bull Soc. franç. de dermat, et syph. **35**:486, 1927; (*b*) Use of Tubular Grafts from Scalp in Extensive Mutilating Lupus Vulgaris, ibid. **39**:712, 1932; (*c*) Surgical Treatment of Lupus Vulgaris by Use of Tubular Cranial Flaps, French M. Rev. **2**:415, 1932. (*d*) Moure, P., and Barraya, C.: Surgical Therapy of Lupus Vulgaris by Transplantation of Tubular Grafts from Scalp, Bull. Soc. franç. de dermat. et syph. **41**: 136, 1934.

13. (*a*) Salomon, A.: Skin Flap Transplantation for Lupus of Neck and Chin, Deutsche med. Wchnschr. **52**:1821, 1926; (*b*) Skin Flap Transplantation for Lupus of Neck and Chin, ibid. **53**:410, 1927.

cent). The types of skin grafts used by these investigators in plastic repair have been free full thickness, pedicle and Thiersch. In contrast to these favorable European reports, however, American investigators employing similar surgical methods for the treatment of lupus vulgaris have reported almost uniform failure in their cases, because of postoperative recurrence of lupus nodules in the skin graft or scar. Van Rhee, in 1927,[10a] reported the recurrence of lupus vulgaris five years after the skin graft was employed in a facial patch of lupus vulgaris. Traub and Kice, in 1933,[10b] reported the complete excision of a patch of lupus vulgaris on the face early in the disease, followed by replacement skin graft. There was recurrence in this patient not only about, but in, the graft. Brock, in 1937,[10c] reported the surgical diathermic excision of a lupus vulgaris patch on the neck of a 21 year old woman, with occurrence of ten small red-brown nodules in the healed wound about the graft. O'Leary, in 1939 [10e] and 1946,[14] listed 3 cases and stated that his experience at the Mayo Clinic in excision and grafting in lupus vulgaris was unsatisfactory and that this method of treatment had been abandoned. O'Leary stated that even in cases with a small beginning patch of lupus vulgaris in which the possibilities of cure appeared ideal, there was recurrence in the scar or a recurrence of the disease in the graft. Traub, in 1940,[10f] reported failure in 2 of 3 cases of lupus vulgaris in which plastic surgical treatment was employed. Montgomery, in 1944,[10i] wrote of a case of lupus vulgaris in which plastic repair was employed, with excellent immediate results but with subsequent development of extensive lupus nodules in the skin graft. Ormsby [15] stated that his experience with plastic surgical treatment of lupus vulgaris was unfavorable in 1 patient. Lupus nodules reappeared in this patient in the grafted area postoperatively within several months, and the disease became as extensive within a year or two as before the operation. Eller,[15] reported unsatisfactory experience with surgical treatment in 2 cases, because of recurrence of the disease in the grafted areas. It is of interest that a recent personal communication from Dr. Svend Lomholt, director of the Finsen Institute in Copenhagen, Denmark, revealed that his experience with plastic surgical treatment for lupus vulgaris was unsatisfactory, because recurrence in the graft was common. Dr. Lomholt's remarks are of especial value when compared with most European reports, because the Finsen Institute in Copenhagen is one of the oldest and largest treatment centers for lupus vulgaris in Europe.

14. The University of Minnesota School of Medicine, Rush Medical College of the University of Illinois, Northwestern University Medical School, The New York Postgraduate Medical School of Columbia University, The University of Michigan Medical School, Harvard University Medical School, The University of Pennsylvania Medical School.

15. Personal communication to the authors.

Hollander and Shelton [10d, h] and Maliniac [10g] are American investigators who have reported successful results in the treatment of lupus vulgaris with surgical excision and plastic repair. A personal communication from Dr. Hollander in 1946 revealed that there had been a recurrence of the disease in 1 of his patients suffering from extensive cutaneous tuberculosis following surgical excision and pedicle grafting. Hollander attributed this failure to the impossibility of resecting enough skin to insure disease-clear edges. He expressed the belief that surgical treatment offers the best results in the nonhematogenous type of cutaneous tuberculosis. Crawford [15] stated that at the Massachusetts General Hospital surgical extirpation of lupus vulgaris has now replaced other forms of treatment when practicable. A radical surgical procedure is used, and the results have been excellent if sufficient margin is allowed and if the tissue is removed down to the fascia. According to Crawford all thoughts of cosmetic surgical measures must be disregarded in this procedure. If suitable plastic closure is not feasible at the time, subsequent attempts can be made. The only failures reported by Crawford have been in those patients in whom the diseased tissue was too extensive to remove completely and in those in whom extirpation was not sufficiently radical.

Because lupus vulgaris is often a hematogenous type of cutaneous tuberculosis, the frequent American reports of recurrence of the disease after surgical extirpation and plastic repair are readily understood. The recurrence of the disease in situ after a surgical technic employing wide and deep excision indicates that the disease is probably of systemic origin. Michelson [15] expressed the opinion that lupus vulgaris is a disease which local treatment does not cure and stated that "the solution of the problem of treatment for lupus vulgaris lies in treating the patient and not the local area." The unfavorable results obtained by the majority of American dermatologists with local treatment for the disease by surgical excision followed by skin grafting would tend to confirm Michelson's viewpoint. We are in agreement with Michelson and advise the abandonment of local surgical treatment of lupus vulgaris alone and the adoption in its stead of an internal etiologic approach in the treatment of this disease. If surgical measures are employed, they should be combined with internal modes of treatment, as for systemic tuberculosis. Perhaps the internal type of treatment recently introduced by Charpy,[16] consisting of the administration of large doses of vitamin D (irradiated ergosterol), autohemotherapy and other proved methods of treatment for internal tuberculosis, alone or combined with plastic surgical repair, offers the solution to the problem of treatment for lupus vulgaris.

16. Charpy, J.: Apropos du traitment du lupus tuberculeux; une question de priorite, Ann. de dermat. et syph. **5**:317, 1945.

SUMMARY AND CONCLUSIONS

A case of lupus vulgaris is reported in which treatment with surgical excision and replacement skin graft was followed by recurrence of the disease in the skin graft and scar.

A review of the medical literature shows that despite the favorable reports from European investigators, a state of confusion exists in the United States as to the value of the surgical treatment of lupus vulgaris, because of frequent postoperative recurrence of the disease.

A survey of dermatologic centers in the United States as to the value of the surgical treatment of lupus vulgaris indicates that the majority of American dermatologists have had unsatisfactory results in the surgical treatment of this disease, because of frequent postoperative recurrence of nodules of lupus vulgaris.

Since lupus vulgaris is frequently hematogenous in origin, we advise that if local surgical treatment is employed for the disease it should be combined with treatment of internal causative factors, as for systemic tuberculosis.

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"REPEAT" CULTURES IN DERMATOPHYTOSIS

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MANY years ago, Mitchell stated picturesquely that when there were failures in the culture of scrapings from the toes, the attempts should be repeated "not seven times, but seventy times seven." Still, most texts treat only superficially or not at all of the necessity of using discrimination and care when selecting cutaneous scrapings for microscopic examinations and of collecting and planting an abundance of material when the cultures are essayed. Doubtless some dermatologists are aware of this, but many of them do not practice it. In any event, it is a common experience in the Laboratory of Dermatological Research at the University of Pennsylvania to receive a dozen or less particles of scrapings, perhaps crushed and adherent between two glass slides which are bound together with rubber bands, with the request that both microscopic examination and culture be performed. This is not serious in the case of material from lesions of tinea circinata and capitis, in which the fungus is usually present in abundance and is more or less uniformly distributed throughout the lesion, but in the case of ringworm of the toes and nails the inadequacy of material is usually fatal to success. This is discouraging to practitioners and mycologists alike.

Doubtless this experience is shared by mycologists in general. In such circumstances it is possible to do no more than go through the motions of the tests, with only faint hopes of success, and one is surprised when positive results are achieved. In short, practitioners must do their part by supplying the scrapings in proper and adequate amount, otherwise negative results will be secured which are meaningless one way or the other. We appreciate that this may appear to be a trifling matter, but experience has shown that it is not, when weighed in terms of results.

A recent experience during certain studies of dermatophytosis [1] has supplied concrete data in respect to cultures that are so outstanding

From the Laboratory of Dermatological Research, University of Pennsylvania.

that it points up the matter and justifies this appeal for more general observance of the appropriate directions for the collection and planting of materials. Too, it illustrates the necessity for the repetition of attempts at culture, even to the point of exhausting all of the material available. Lewis and Hopper[2] recently touched on this point. In order to supply a working guide to practitioners as well as laboratory workers, the following method is the one that we have followed. Throughout, the keynote is "discrimination and care." A hit or miss attitude will result in a high percentage of negative cultures.

COLLECTION OF SCRAPINGS

In all cases the lesion is well wetted and rubbed with alcohol and the materials collected immediately after drying. In the case of small lesions the entire surface should be denuded; no harm can be done, and the chances for success are increased if the physician is not too hurried. It may be necessary to use scissors in the case of larger tags of skin that are persistently adherent at the margin of the lesion. These are decidedly worth the effort to secure.

Tightly adherent thick hyperkeratotic lesions ("soft corns") pose a special problem. The skin around them should be scraped centripetally —against the grain, as it were. Thereby a peripheral shelf of keratinous substance will be raised, and by prying and tearing it upward the entire lesion can be loosened and partly or entirely removed. Considerable force may be necessary here, together with the assistance of forceps and perhaps scissors, but in any event, a goodly portion of the lesion can be secured. This is transferred to a sheet of clean paper and snipped with scissors into small slivers and cubes while still moist. This should be done at once, because when dry the particles spring about and can be largely lost.

Vesicular lesions, as of the soles, are transfixed by a dressmaker's needle. Using this as a handle, the lesion is pulled upward as far as is possible without tearing. Fine curved scissors are now introduced below the needle, and the roof of the vesicle is snipped off. Depending on size, it can then be divided into several portions. Incidentally, physicians should keep in mind which side of the roof is "up" and which is "down," because, when it is arranged on the slide for microscopic examination, its inferior surface should be "up" (fungus will be more readily visible when in contact with the coverslip). Vesicular fluid is so inferior in value that, by and large, it need not be considered as a useful source of material.

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1. Weidman, F. D., and Glass, F. A.: Dermatophytosis and Other Forms of Intertriginous Dermatitis of the Feet, Arch. Dermat. & Syph. **53**:213 (March) 1946.

2. Lewis, G. M., and Hopper, M. E.: Concurrent, Combined and Consecutive Fungous Infections of the Skin, Arch. Dermat. & Syph. **47**:27 (Jan.) 1943.

Real uncertainties arise in the case of the diffuse dusky lesion of the "moccasin" area due to Trichophyton purpureum, with its thin and tightly adherent scales. Here it is difficult to estimate where the processes are the more acute.

Fortunately, though, the problem is not large in the case of the more extensive and acute lesions of tinea cruris. Here it suffices to remember that the peripheral erythematous parts or any satellite lesions that may be present are the ones to be selected for scraping.

Incidentally, the percentage of positive cultures secured from different types of lesions was as follows, which may indicate which types are the more promising, in the order given; macerated 75 per cent, vesicles 60 per cent, hyperkeratotic (between toes) 54 per cent and erythematous (and/or scaly) 35.6 per cent.

As to the apparatus for securing scrapings, we use a small scalpel the handle of which has been cut to a length of 1½ inches (about 3.8 cm.); the blade can be manipulated to better advantage without the long handle. For receiving and transmitting materials, squares of black paper about 3 inches (about 7.6 cm.) wide are employed (wrappings of photographic negatives); this supplies a contrasting background when handling the particles in the laboratory. If the materials are moist, they should be allowed to dry partly on the paper before folding, otherwise pressure will glue them to it. Thereafter they should be gently loosened if they have become attached to the paper. This precaution will prevent loss of valuable material during examinations in the laboratory, because the forcible disengagement of materials may cause the particles to spring away from the paper.

CULTURE

Materials and Methods.—We are recording these data in a manner that may appear unnecessarily detailed. However, this is justified in view of the high percentage of positive cultures that we secured and because the reader may be curious as to the circumstances in which we secured such good results.

The patients were inmates of a penitentiary, which made it possible to secure numerous lots of scrapings within a short period of time (Nov. 10-24, 1942) and thus assure uniformity in the conditions of culture (season, temperature, dryness and composition of culture mediums). At this particular time of the year there were not any extensive acute eczematoid lesions; nearly all were quiescent. Incidentally, 27.7 per cent of the patients had treated their lesions within the preceding two weeks, according to either professional or self prescription. In all, one hundred and seventy-one samples of scales were collected from 155 patients. Most samples were from the toes: five came from the groin, and there were 13 patients in whom more than one region of the

body supplied the materials. Usually generous amounts were taken and planted. Sowings were made in 6 by 1 inch (15 by 2.5 cm.) test tubes on a modified Sabouraud's test medium, which has been designated "Pennsylvania medium" [3] (containing Fairchild's peptone [4] and crude American dextrose), and kept at room temperature in diffuse daylight (November 1942). Microscopic examinations of scrapings were not made, because this particular study concerned the treatment of intertriginous dermatitis, not dermatophytosis in particular; it was the identity of the fungus, and not the mere presence or absence of fungus, that was of significance in our studies.

Results.—From the first set of one hundred and seventy-one plantings, cultures of pathogenic fungi were secured in 29.2 per cent. From the (one hundred and one) remnants of scrapings which had negative results, nine positive cultures were obtained (8.9 per cent). This means that by making such a second set of plantings, a positive culture can be expected in about 5 per cent of the cases. Roughly, thus 35 per cent of the entire series of plantings eventually resulted in positive culture. This is a high figure, but it has been exceeded; Legge and his co-workers obtained 39 per cent [5] and Epstein and Snell 44 per cent.[6] (Similar studies of cultures were conducted at a second penitentiary. The series of patients was smaller [70]. We secured 41 per cent of positive cultures at the first planting; second plantings were not made.) Incidentally, 68.3 per cent were Trichophyton interdigitale (gypseum), 30 per cent T. purpureum and 1.66 per cent Epidermophyton inguinale (floccosum) (only 1 case).

CONCLUSIONS

1. If the fullest benefits are to accrue from attempts at culture, utmost pains and discrimination must be exercised in the collection of scrapings.

2. Whether due to the conditions peculiar to institutions or not, it is possible, on occasion, to secure cultures from dermatophytosis in as high percentages as 35, 39 and 44.

3. The addition of nearly 5 per cent positive cultures secured in our second set of plantings indicates that it is indeed worth the effort to repeat plantings.

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3. Weidman, F. D.: The Laboratory Aspects of Dermatophytosis, Arch. Dermat. & Syph. **15**:659 (April) 1927.

4. This is no longer on the market. At present we use the Difco brand of peptone.

5. Legge, R. T.; Bonar, L., and Templeton, H. J.: Epidermomycosis at the University of California, Arch. Dermat. & Syph. **27**:12 (Jan.) 1933.

6. Epstein, S. S., and Snell, F. D.: Gentian Violet in Sabouraud's Medium for Isolation of Pathogenic Fungi, Arch. Dermat. & Syph. **42**:308 (Aug.) 1940.

STUDIES ON SENSITIVITY TO PLASTICIZERS

Ortho-Nitrobiphenyl, N-Isopropyl Benzene Sulfonamide and N-Isopropyl Benzene Sulfonamide and N-Isopropyl Ortho and Para Toluene Sulfonamide

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PLASTICIZERS are important materials in the manufacture of plastics from synthetic resins. They are added to the resins to introduce new physical properties. Selection of the proper plasticizer may decrease the brittleness, improve the flow or change the melting point of the resin.

Dermatitis occurs in workers engaged in the manufacture of synthetic resins and in persons using the finished materials. In a comprehensive survey of the subject, Schwartz [1] wrote of the causation of dermatitis from these resins. He stated that dermatitis was of frequent occurrence among workers in the industry, but was not usually caused by the finished product. He expressed the belief that the usual causes of dermatitis were the basic materials from which the resin was made, the incompletely condensed resin, the uncombined components and the catalysts or the by-products. For example, during the manufacture of any phenol-formaldehyde resin the phenol or the formaldehyde may cause dermatitis. If the plasticizers used are cutaneous irritants or sensitizers they may cause dermatitis during the manufacturing process or after the use of the finished product. Dermatitis has occurred from the wearing of wrist watch straps made from a polyvinyl plastic.[2] The actual irritants in the straps were found to be the plasticizers and stabilizers which were added to the resin.

Funds and material for this study were supplied by the Monsanto Chemical Company, St. Louis.

Studies, observations and reports from the Dermatological Department of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University.

1. Schwartz, L.: Dermatitis from Synthetic Resins, J. Invest. Dermat. **6**:239-255 (Aug.) 1945.

2. Zeisler, E. P.: Dermatitis from Elasti-Glass Garters and Wrist Watch Straps, J. A. M. A. **114**:2540-2542 (June 29) 1940.

Patch tests were performed with a group of plasticizers in an attempt to determine the effects of these materials on the human skin.

I. PLASTICIZER ORTHO-NITROBIPHENYL

The ortho-nitrobiphenyl that was used for testing is a general purpose plasticizer and may be used with nearly every type of synthetic resin. It is a light yellow to reddish liquid, with a characteristic fruity odor. The final testing was performed with a 5 per cent solution in acetone, because the material was insoluble in water. This solution was used because the manufacturer estimated that this is the concentration to which workers in the industry are likely to be exposed.

II. PLASTICIZER N-ISOPROPYL BENZENE SULFONAMIDE

N-isopropyl benzene sulfonamide is sold under the trade name "santicizer 130." It is a colorless liquid, with a slightly fruity odor. It may be added to many plastics, the chief advantage being that it will impart toughness, high gloss and good flow to the finished product. This plasticizer is soluble in 70 per cent alcohol. A solution was made of 5 per cent n-isopropyl benzene sulfonamide in 70 per cent alcohol.

III. PLASTICIZER N-ISOPROPYL BENZENE SULFONAMIDE PLUS N-ISOPROPYL ORTHO AND PARA TOLUENE SULFONAMIDE

A mixture of n-isopropyl benzene sulfonamide and n-isopropyl ortho and para toluene sulfonamide is sold under the trade name "santicizer 131." It is a colorless liquid, with a slightly fruity odor. It may be used in exactly the same plastics and for the same purposes as "santicizer 130." Since this mixture is soluble in 70 per cent alcohol a solution was used consisting of 5 per cent of the mixture in 70 per cent alcohol.

PROCEDURE IN PATCH TESTS

The patch tests with the plasticizers were performed according to the procedure recommended by Schwartz and Peck.[3] The technic used in this particular testing has been designated as the "prophetic patch test" technic. This type of testing is recommended for the purpose of foretelling whether a substance will or will not produce dermatitis after contact with the skin. In addition, possible irritant qualities of chemicals or other articles coming in contact with the skin can be determined by means of this test. Two separate tests are made, ten to fourteen days apart, on the same person. Two hundred persons are used, just as in

3. Schwartz, L., and Peck, S. M.: The Patch Test in Contact Dermatitis, Pub. Health Rep. **59**:546-557 (April 28) 1944.

other standard testing. It is presumed that reactions will occur in the first series if the substance tested is a primary irritant, provided that the person under observation had never had previous contact with the substance. The reactions observed after the second series of tests indicate the number of persons in whom sensitivity has been induced by the first patch test.

A group of 200 volunteers was tested with each plasticizer. The solvent in full strength was used as the control. The volunteers were factory employees and patients at two St. Louis hospitals. No patient with cutaneous or systemic disease was tested. The ages of the volunteers ranged from 15 to 70 years. The sexes were equally represented. Only 1 of the volunteers was Negro.

Technic.—1. Ortho-nitrobiphenyl (5 per cent in acetone) and acetone (full strength), as the control, were applied to pieces of gauze 0.25 inch (0.6 cm.) square and covered with standard "elastopatch" (Duke Manufacturing Co.). N-isopropyl benzene sulfonamide (5 per cent in 70 per cent alcohol) and alcohol (70 per cent), as the control, were applied to pieces of gauze 0.25 inch (0.6 cm.) square and covered with standard "elastopatch." The mixture n-isopropyl benzene sulfonamide and n-isopropyl ortho and para toluene sulfonamide (5 per cent in 70 per cent alcohol) and alcohol (70 per cent), as the control, were applied to pieces of gauze 0.25 inch (0.6 cm.) square and covered with standard "elastopatch." 2. The patches were placed on the scapular and infrascapular areas, the back of the arms and the anterior and internal surfaces of the thighs. 3. The patches were removed approximately forty-eight hours later and the areas observed. The areas were again observed in ninety-six and one hundred and ten hours after the removal of the patches. 4. Ten or more days after the patches were removed, fresh ones were applied at the same sites, and steps 2 and 3 were repeated.

RESULTS

There were no positive reactions to the patch tests with the three plasticizers, ortho-nitrobiphenyl, n-isopropyl benzene sulfonamide and n-isopropyl benzene sulfonamide and n-isopropyl ortho and para toluene sulfonamide (mixture) or to the control solutions. Henderson and Riley [4] have applied statistical principles to the results obtained from patch tests. According to their formula, if no positive reactions in patch tests are observed in 200 subjects, the maximum rate of positive reactions in the population from which the sample was drawn will be

4. Henderson, C. R., and Riley, E. C.: Certain Statistical Considerations in Patch Testing, J. Invest. Dermat. **6**:227-230 (June) 1945.

1.5 per cent. They express this estimate at the likelihood level of 95 per cent; that is, the estimate is expected to agree with the results obtained from the testing of an entire population 95 per cent of the time.

SUMMARY

An attempt to produce sensitization was unsuccessful in 200 volunteers who were tested with each of the three plasticizers: ortho-nitrobiphenyl, n-isopropyl benzene sulfonamide and n-isopropyl benzene sulfonamide and n-isopropyl ortho and para toluene sulfonamide (mixture). There was no evidence of preexisting sensitivity to these plasticizers in the volunteers.

EFFECTS OF TOPICAL APPLICATIONS OF DIPHENHYDRAMINE HYDROCHLORIDE (BENADRYL)

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THE POWERFUL antihistamine action of "benadryl hydrochloride" N. N. R. (diphenhydramine hydrochloride) has been repeatedly demonstrated in animals [1] and in human beings [2] with [3] and without [4] allergic diseases. The frequency of the side effects of the drug, when

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(Footnotes continued on next page)

given in adequate amounts by mouth, has led to the following investigation of its topical use for diseases in which cutaneous manifestations of a probably allergic nature are present.

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Diphenhydramine hydrochloride has been applied topically in four different ointment bases and in strengths of 2 and 5 per cent, as listed in table 1.[5]

METHODS AND RESULTS

Influence of Diphenhydramine Hydrochloride Ointments on the Histamine Flare and Wheal Reaction in Persons Having no Known Allergic Disease or Other Diseases Associated with Recognizable Disturbances of the Autonomic Nervous System.—Four tests were performed simultaneously on the skin of each of 63 subjects (28 male and 35 female) on two separate sites on the volar surface of each forearm.

Control Test (I): To examine the cutaneous sensitivity to histamine, a drop of a 0.1 per cent solution of histamine diphosphate was applied to the volar surface of the forearm after cleansing it with alcohol and ether. A slight depression of the skin under the drop was then made by pressure with a sterilized straight pin, care being taken not to cause any bleeding. After five minutes, the drop was carefully wiped away and the size and shape of the wheal and the site of erythema were outlined with ink. A permanent record of this outline was made by tracing it with india ink on transparent paper; a second similar record was made at the end of ten minutes. The size of the wheal and of the site of erythema were approximated by multiplying the

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5. All supplies of "benadryl" and ointments 1 and 2 were furnished by Parke, Davis & Company, Detroit, through Dr. E. A. Sharp, Director of Clinical Investigation. The ointment base, "amerchol," was supplied by the American Cholesterol Products Co., Milltown, N. J., through I. J. Drekter.

diameters at right angles. The values thus obtained in each subject were arbitrarily designated as 100 per cent, and the reactions in all test sites, similarly calculated, were expressed in percentages of this control (table 2).

Diphenhydramine Hydrochloride Ointment Alone (II): A simple needle prick, as for the histamine test, was made on the volar surface of one forearm, and a bit of ointment, the size of a pea, gently massaged into the area for about five minutes. A small wheal without erythema was observed in 3 subjects, but this was sharply distinguishable in size and duration from the histamine control test in the same persons (table 2).

TABLE 1.—*Ointments Used in Cutaneous Tests with Histamine*

Ingredient	Percentage (Approximate)
Ointment 1 (wool fat and petrolatum)	
"Benadryl"	5.0
Water	10.0
Wool fat, anhydrous, odorless	15.0
White petrolatum	70.0
Ointment 2 ("carbowax")	
"Benadryl"	2.0
"Carbowax 1500" monostearate q. s. ad	100.0
Ointment 3 ("amerchol") (5%)	
"Benadryl"	5.0
Agnosterol	
Lanosterol more than	6.0
Ceryl alcohol	
Cetyl alcohol	
Cholesterol (pure alcohol)	4.0
Hydrocarbon mixture derived from petrolatum q. s. ad	100.0
Ointment 4 ("amerchol" in water) (5%)	
"Benadryl"	5.0
Water	30.0-40.0
"Amerchol"	55.0-65.0
Ointment 5 ("amerchol" in water) (2%)	
Same as ointment 4, except that the resultant mixture contains 2 per cent "benadryl"	

Diphenhydramine Hydrochloride Ointment Applied After Histamine (III): The ointment was applied four to five minutes after the histamine reaction was produced (A). The procedure of the control histamine reactions was simulated in every way except that from four to five minutes after the pinprick ointments, as subsequently noted, were gently massaged into the area as described under test B (table 2).

In 4 subjects, ointment 5 (2 per cent diphenhydramine hydrochloride in a sterol base containing pure cholesterol and other closely related alcohols from wool fat ["amerchol"] and water) had no appreciable effect on the course of the histamine response. Ointment 4 (5 per cent diphenhydramine hydrochloride in "amerchol" and water) gave uncertain results in 6 patients. No effort was made to perform any further tests with either of these ointments.

Tests with ointment 3 (5 per cent diphenhydramine hydrochloride in "amerchol") were made on 6 subjects. Itching was relieved within one minute following the beginning of the application of the ointment, and the duration of the flare and wheal reaction was reduced to six minutes. This is in sharp contrast to an average duration for the

TABLE 2.—*Influence of Ointments Containing "Benadryl" on the Triple Response of the Skin to Histamine*

Test Designation	Nature of Test (Ointment No.)	Number of Subjects	Average Responses (Percentage of Control)				Comment
			Wheal		Flare		
			5 Min.	10 Min.	5 Min.	10 Min.	
I	Control (histamine alone, 0.1%)	63	100.0	100.0	100.0	100.0	Reaction always lasted more than 20 min.
II	Control* (ointments 1, 2, 3, 4 and 5, respectively)	63	0	0	0	0	
III	A. Histamine followed in 4-5 min. by 4-5 min. massage with:						
	(*a*) 2% "benadryl" in "amerchol" and water (5)	4	98.7	100.6	101.4	94.8	
	(*b*) 5% "benadryl" in "amerchol" and water (4)	6	103.4	97.0	96.5	100.0	
	(*c*) 5% "benadryl" in "amerchol" (3)	6	39.3	0	50.0	0	Reaction over in 6 min.
	(*d*) 5% "benadryl" in wool fat and petrolatum (1)	11	70.7	3.4	64.9	2.7	Entire reaction gone in 10 subjects at 10 min.
	B. Histamine followed in 0.5 min. by 0.5 min. massage with:						
	(*a*) "Benadryl" in wool fat and petrolatum (1)	30	85.3	32.0	65.6	23.9	
	(*b*) 2% "benadryl" in "carbowax 1500" monostearate	6	80.4	38.7	73.0	40.2	
IV	Histamine preceded by 4 to 5 min. massage with:						
	(*a*) 5% "benadryl" in wool fat and petrolatum (1)	11	0	0	0	0	
	(*b*) 2% "benadryl" in "carbowax 1500" monostearate (2)	11	0	0	0	0	
	(*c*) 5% "benadryl" in "amerchol" (3)	6	0	0	0	0	

* The ointment used corresponded in each instance to that employed over sites of tests III and IV.

control reactions of not less than twenty minutes in these same subjects. The reaction disappeared completely in 2 of the 6 subjects at the end of five minutes, and the average reduction for the whole group was more than 50 per cent of the control (table 2).

In 11 subjects, ointment 1 (5 per cent diphenhydramine hydrochloride in wool fat and petrolatum) was used. At the end of about five minutes the wheal was reduced to an average of 70 per cent of that

of the control and the erythema to 65 per cent. At the end of ten minutes the entire reaction had disappeared, as compared with a reaction lasting more than twenty minutes for the control or test I.

Test III B, a variant of test III A, was carried out in 30 subjects with ointment 1 and in 6 subjects with ointment 2 by wiping away the excess fluid used in the histamine test at the end of thirty seconds rather than at the end of from four to five minutes. Immediately after this, diphenhydramine hydrochloride ointment was gently massaged into the test area for one-half minute only. The resulting wheals and flares of the control and test areas were compared at the end of five and ten minutes, respectively. The average size of the wheal and flare reactions with ointment 1 at the end of five and ten minutes, respectively, expressed in percentages of the corresponding histamine controls, were 85.3, 65.6, 32.0 and 25.9, respectively (table 2). When ointment 2 was employed, these figures, in the same order as previously noted, were 80.4, 73.0, 38.7 and 40.2, respectively.

Diphenhydramine Hydrochloride Ointment Applied Before the Histamine Test (IV): In this group of tests, the procedure of test III was reversed, that is, the ointment was massaged into the test area for four or five minutes before the histamine was introduced. With ointment 3 (5 per cent diphenhydramine hydrochloride in "amerchol"), the wheal and flare were completely abolished in the 6 subjects tested (table 2). With ointments 1 (diphenhydramine hydrochloride 5 per cent in wool fat and petrolatum) and 2 (2 per cent diphenhydramine hydrochloride in "carbowax 1500" monostearate), each of 11 subjects showed a suppression of the flare and wheal (table 2). A similar result was obtained with ointment 3, so that no further tests of this type were done (table 2).

After the aforementioned experiments, the question was raised as to whether or not the massaging and the presence of the ointment bases might not materially influence the course of the histamine wheal and flare response. With this in mind, three histamine tests were performed simultaneously on each of 5 subjects. However, prior to the application of histamine one area was gently massaged for about four to five minutes with the "carbowax 1500" monostearate base of ointment 2 and a second area with the cholesterol base of ointment 3. The third site served as control. While some variation in the size and shape of the response was observed from subject to subject and from site to site, these did not appear to be statistically significant. In any given case the variation did not exceed plus or minus 10 per cent for either the wheal or the flare. It was concluded that the results in the previous tests could, with reasonable certainty, be looked on, therefore, as due to the diphenhydramine hydrochloride incorporated in the ointment rather than to the massage or to any antihistamine activity inherent in the ointment bases themselves.

Only one reference has been made thus far to the itching which almost invariably accompanied the response to the action of histamine on the skin. It was relieved promptly, usually within one minute, in all of the tests in which any decrease in the size of the wheal or flare as compared with the control was noted.

Influence of Topical Applications of Diphenhydramine Hydrochloride on Various Itching Dermatoses.—In clinical trial for the relief of certain dermatologic diseases, ointments 1 and 2 have been used (tables 3 and 4). Wherever possible, the ointment base, entirely free of diphenhydramine hydrochloride was employed as a control. As a rule, this was done by applying the base alone to one area of the body and the

TABLE 3.—*Influence of Five Per Cent "Benadryl" Ointment (Wool Fat and Petrolatum Base) on Dermatoses Associated with Pruritus*

		Itching *						Effect on Progress of Underlying Lesion *		
					Relief from Single Application (Hr., Approx.)					
Disease	Number of Cases	C. R.	I.	N. R.	Initial	Duration	Local Irritation (No. Cases)	C. R.	I.	N. R.
Atopic dermatitis	16	8	4	4	0.03-0.25	0.5-4	Burning (1) Itching (2) Rash (1)	2	8	6
Neurodermatitis	4	1	2	1	0.08-0.25	1-6	Burning (2) Weeping (1)	0	2	2
Poison ivy	25	20	5	0	?	Several	.....	25	0	0
Other contact dermatitis	3	0	1	2	....	.....	Burning (1)	0	0	3
Pruritus vulvae	2	1	0	1	0.15	1-4	Burning (1)	0	1	1
Pityriasis rosea	1	0	1	0	0.5	2	.....	..	?	..
Psoriasis	3	1	2	0	?	Several	.....	0	0	3
Angioneurotic edema	1	1	0	0	0.15	.....	.....	0	1	0
Senile eczema	1	0	1	0	0.25	2-3	.....	0	?	0
Total	56	32	16	8				27	12	15

* C. R. is complete relief, I is improvement and N.R. is no relief.

diphenhydramine hydrochloride to another, preferably symmetrically placed, area of equal size and degree of involvement. However, in many instances, particularly in the majority of the cases of dermatitis due to poison ivy, no control ointment was used.

Results with Ointment 1 (Five per Cent Diphenhydramine Hydrochloride in a Wool Fat and Petrolatum Base): The 5 per cent diphenhydramine hydrochloride ointment was applied to the itching dermatoses of 56 persons (table 3). Itching was completely relieved in 32, partially relieved in an additional 16 and not affected in 8. Twenty-two of the 32 patients whose itching disappeared showed also complete relief of the underlying cutaneous manifestation. This figure includes 20 patients with the self-limiting condition, poison ivy. Of the 2 cases of atopic eczema in which there was complete relief, 1 was proved due

to cat dander and the other was a childhood eczema due to milk. The rash was completely controlled in both instances by the diphenhydramine hydrochloride ointment, but that it did not return on the discontinuance of treatment is probably due to the fact that the offending allergen was removed as far as possible from the environment. From these data it is clear that diphenhydramine hydrochloride plays an auxiliary role in the relief of the itching, thus improving the patient's tolerance for his disease during more fundamental treatment. The recorded responses of a wide variety of diseases to diphenhydramine hydrochloride suggests a somewhat common cause for itching in highly diversified dermatologic diseases.

TABLE 4.—*Influence of Two Per Cent "Benadryl" Ointment ("Carbowax 1000" Monostearate Base) on Dermatoses Associated with Pruritus*

		Itching *							
					Relief from Single Application (Hr., Approx.)			Effect on Progress of Underlying Lesion *	
Disease	Number of Cases	C. R.	I.	N. R.	Initial	Duration	Local Irritation (No. Cases)	C. R.	I.	N. R.
Atopic dermatitis	8	4	2	2	0.1-0.3	1-6	Burning (1)	2	2	4
Neurodermatitis	2	1	0	1	....	.....	.....	0	0	2
Contact dermatitis	2	1	0	1	0.25-0.30	1-3	.....	0	0	2
Chronic urticaria	1	1	0	0	0.08-0.25	1-2	.....	0	1	0
Hypostatic eczema (varicosities)	2	2	0	0	0.25-0.50	2-4	.....	0	2	0
Dermatitis medicamentosa	2	2	0	0	0.25-0.30	4-12	.....	2	0	0
Senile eczema	1	1	0	0	0.25-0.50	2-4	.....	1	0	0
Total	18	12	2	4				5	5	8

* C. R. is complete relief, I is improvement and N.R. is no relief.

For instance, by relieving the itching of dermatitis due to poison ivy, we believe that the usual course of the disease was shortened by from one to three days. In all instances of rhus poisoning the severity of the lesions was decreased by the use of the ointment.

Although no attempt has been made to include them statistically in this report, it has been shown that the pruritus, wheal, flare and more widespread manifestations frequently following bee stings and mosquito bites were decidedly improved by the use of the 5 per cent ointment.

The duration of relief from itching following a single application of the ointment varied considerably from patient to patient, from disease to disease and often in the same patient from time to time (table 3). Improvement was usually noticed in from five to fifteen minutes and lasted from one-half hour to several hours, irrespective

of the nature of the disease. Persons with neurodermatitis, if improved at all, showed the longest periods of freedom from itching.

The question of the role of the ointment base itself in the degree of relief obtained was partially answered by the use of a control ointment from which diphenhydramine hydrochloride was excluded. Each person served as his or her own control. The ointment base was applied to one group of lesions and the base plus 5 per cent diphenhydramine hydrochloride to a second. Whenever practical, symmetrically located sites were used and lesions of as nearly equal severity as possible selected. In this way the influence of the drug was tested in a total of 8 subjects—in 2 of the patients with atopic dermatitis, in all 4 with neurodermatitis, in 1 with contact dermatitis involving the hands and in 1 with senile eczema. One of the patients with neurodermatitis saw no difference between the base and the diphenhydramine hydrochloride-containing ointment. All the rest expressed the belief that the lesions to which the diphenhydramine hydrochloride was applied were the more improved and itched less.

Five patients complained of burning following the use of the ointment. In 4 this disappeared within several minutes and was followed by a soothing effect, but in 1, a patient with atopic dermatitis, the burning was so severe as to preclude its further use. Itching was aggravated in 2 patients, both of whom had open lesions, and "weeping" of the lesion was increased in 1 of these, a patient with neurodermatitis. In 1 patient with atopic dermatitis there was a sensitivity to wool fat, and both the diphenhydramine hydrochloride ointment and the ointment base caused this patient distress.

In all, 48, or 85.7 per cent, of all the patients obtained partial or complete relief of itching, while a smaller but appreciable number had recession of the cutaneous manifestations while using diphenhydramine hydrochloride (table 3). Six patients experienced an untoward reaction to the ointment which was in one instance proved to be due to the wool fat.

Results with Ointment 2 (Two per Cent Diphenhydramine Hydrochloride in a "Carbowax 1500" Monostearate Base): Fourteen of 18 patients (77.8 per cent) with an itching dermatosis (table 4), to the lesions of which the 2 per cent ointment was applied, obtained partial or complete relief of the pruritus. Ten of the 18 (55.6 per cent) showed a partial or complete recession of the dermic lesions while under treatment with the ointment. The number of cases in any one category is too few to draw significant conclusions, but the distribution of results is not unlike that observed for 5 per cent diphenhydramine hydrochloride in the wool fat and petrolatum base. With the 2 per cent ointment, however, irritation of the skin was observed in but one instance. Burning occurred in 1 patient with atopic dermatitis, but

would not have precluded the use of the ointment had it satisfactorily controlled the itching. The duration of effect varied as widely as with the 5 per cent preparation (table 4).

One case of dermatitis medicamentosa was secondary to the injection of diphtheria toxoid and the other to the administration of penicillin. The patient with the rash due to penicillin was comfortable just as long as the ointment was applied twice daily. Most patients prefer much more frequent applications, usually varying from one to four hours apart.

Comparison of the Effects of the Two per Cent and Five per Cent Ointments in Pruritic Dermatoses: Opportunity was afforded to try both ointments in 15 patients—8 with atopic dermatitis, 4 with neurodermatitis, 2 with contact dermatitis and 1 with senile eczema. The 2 per cent ointment was irritative in only 1 instance, a patient with atopic dermatitis. This was a 26 year old woman with a typical distribution of lesions present since childhood. One patient improved while using the 5 per cent ointment and was not affected by the 2 per cent ointment; the 2 per cent preparation relieved the itching and was not irritative. In 3 patients, both ointments helped but the effect was more striking with the 2 per cent strength.

COMMENT

It is clear from the aforementioned results that diphenhydramine hydrochloride is capable of exerting a rather vigorous localized antihistamine action when applied in proper concentration as an ointment to the intact histamine-treated skin. A sterol base containing relatively high concentrations of pure cholesterol and other closely related alcohols from wool fat ("amerchol") appears to be a vehicle superior to a mixture of wool fat and white petrolatum. In limited trial, however, it seems that a "carbowax 1500" monostearate emulsion may prove even more effective than either of these, as 2 per cent concentration of diphenhydramine hydrochloride in this medium showed an activity equal to that of a 5 per cent concentration in wool fat and white petrolatum.

While it is clear from the foregoing that the base used for the ointment makes considerable difference in the quantitative character of the response, it does not in any way alter it qualitatively. Of the bases employed the oil-in-water emulsion ("carbowax 1500" monostearate), in admittedly limited trial, was the most effective. In 2 per cent strength this was effective, whereas the same concentration in a water-in-oil emulsion ("amerchol") seemed to exert almost no antihistamine effect. On the other hand, a 5 per cent ointment in a nonionic oil base (wool fat and petrolatum) was irritative in several instances. It seems, therefore, that satisfactory concentrations for clinical use must lie between these two percentages. None of the bases were irritative per se, except

for an aggravation in 1 patient with atopic eczema, who was sensitive to wool fat. This patient did not tolerate the wool fat and petrolatum mixture, although she could tolerate without distress a mixture of the pure alcohols from wool fat, as are contained in the "amerchol" base.

Fifteen of the patients treated topically had previously obtained some degree of relief from the use of diphenhydramine hydrochloride by mouth. However, several showed some side reaction, usually drowsiness, following its administration in this manner. No systemic reactions of any sort were observed in association with the application of any of the ointments to either an intact or a broken skin.

SUMMARY AND CONCLUSIONS

In 63 subjects the topical application of 2 and 5 per cent concentrations of "benadryl hydrochloride" N. N. R. (diphenhydramine hydrochloride) in ointment bases reduced or completely destroyed the response of the skin to intradermally applied histamine.

"Carbowax 1500" monostearate, an oil-in-water emulsion, appeared to be the best of the three bases employed.

Seventy-four patients with itching dermatoses were treated with ointments containing diphenhydramine hydrochloride. Forty-four, or 59.5 per cent, obtained complete relief from the itching, while an additional 18, or 24.3 per cent, were improved. Six patients experienced some discomfort from the application of the ointment, particularly when a 5 per cent concentration was used. However, in 4 of these subjects this lasted not more than five minutes. Of the other 2, it was due to the base employed in one and to an aggravation of a weeping eczematous disease in the other.

No systemic side reactions were observed in any of the 137 patients who were subjects of this study.

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HERPES ZOSTER ASSOCIATED WITH MONOCYTIC LEUKEMIA

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THE RELATIONSHIP between leukemia and herpes zoster deserves special mention because it is not a relationship of mere chance, but represents rather a definite association. Cases of herpes zoster and leukemia have been reported frequently in the foreign literature, while there have been but few reports in American publications. To date there have been at least 71 cases reported in the world literature. In reviewing these cases one notes that herpes zoster is most frequently observed in patients with lymphatic leukemia and seldom with myeloid leukemia; it has not been reported with monocytic leukemia.

The following case is being reported because it is the first time that herpes zoster has been associated with monocytic leukemia. In addition to being the first time that this relationship has been reported, another significant factor was the observation of monocytic cells in the spinal ganglion and in the intercostal nerves, the site of herpes zoster.

REPORT OF A CASE

R.W., a white American aged 54 and a printer, became ill four years before admission, when weakness, shortness of breath and a productive cough developed. During that time he lost 25 pounds (11.3 Kg.) in weight. For two months prior to his admission he had a sore throat and several attacks of epistaxis. In the past he had the usual childhood diseases and gonorrhea four times.

On entrance the patient appeared well nourished but pale. He was extremely weak, and the skin had a peculiar lemon yellow hue, resembling that of pernicious anemia. The temperature was 99.2 F., the pulse 96 and the blood pressure 128 systolic and 70 diastolic. The pupils were equal and the scleras clear. The left tonsil was enlarged. He was edentulous. On the left lateral side of the chest and back there was an eruption of hemorrhagic herpes zoster, which followed a course parallel to that of several ribs. The lungs were clear, and the heart was not enlarged. A systolic murmur was heard at the apex. The spleen was palpable 2 fingerbreadths below the costal arch, and the edge of the liver was just palpable.

A hemogram revealed the following: hemoglobin 26 per cent, red blood cells 1,360,000 and white blood cells 113,700. The majority of the white cells were immature. Monocytes, monoblasts and many nucleated red cells were observed.

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The hemogram was that of monocytic leukemia. The Kahn reaction of the blood was positive.

The clinical course was fulminating. There soon appeared many petechiae on the soft palate, lips, mouth, trunk and abdomen. Discrete soft palpable lymph nodes appeared in the neck, axillas and epitrochlear and inguinal regions. The nodes varied in size from that of a small pea to that of an almond. The temperature rose steadily to 105 F.; the pulse increased to 150 per minute and the respirations to 55. He died one week after admission to the hospital.

Observations at Autopsy.—External Observations: The body was that of a strongly built fairly well nourished white man. The pupils were moderately

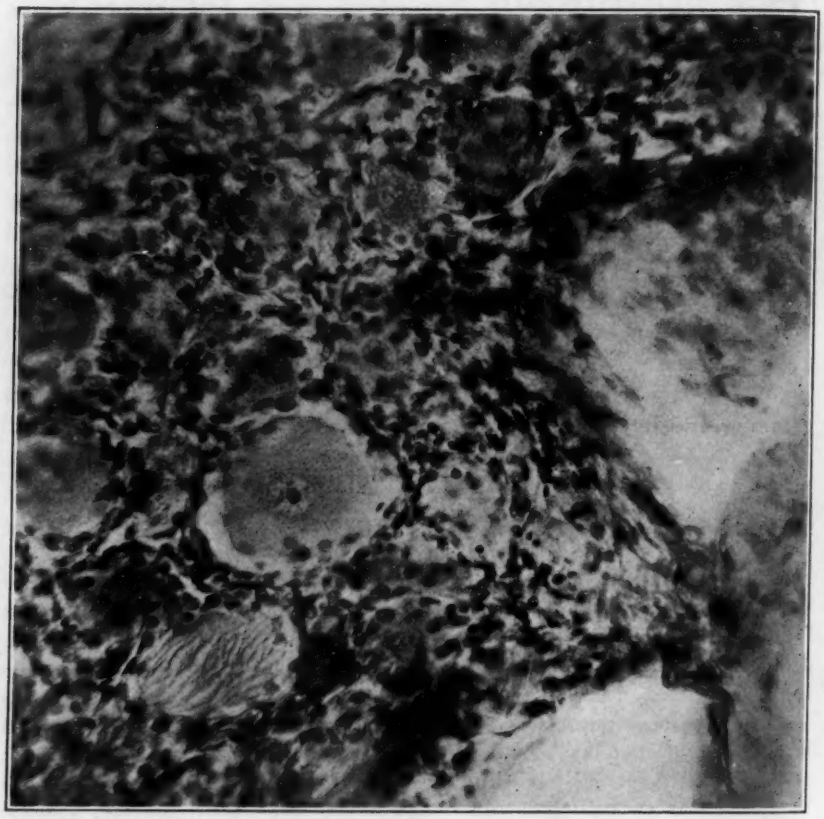

Fig. 1.—Focal accumulations of monocytoid cells in the spinal ganglion.

dilated, round and equal, and on the conjunctiva of the left lower lid were two petechial hemorrhagic areas. Near the inner canthus of the left eye there was a firm nodule, which was centrally ulcerated and about 5 mm. in diameter. The mucosa of the lips and mouth were purplish gray; the teeth were absent. The skin appeared pale and grayish white. Over the chest and upper part of the abdomen were numerous pinpoint-sized to pinhead-sized bright purple-red patches. Extending from the midline of the back anteriorly and downward, in the regions of the sixth and seventh ribs, the skin contained numerous dry and slightly elevated deep purple-red papules, which were up to 3 mm. in diameter and superficially crusted.

Liver: The weight of the liver was 2,515 Gm. The consistency was diminished, the capsule thin and the surface smooth. On sectioning, it appeared pale yellow-gray with lighter yellow lobular centers.

Thoracic Aspect of the Spinal Cord: Left seventh spinal ganglion. Many of the ganglion cells contained dark brown pigment. A few of the ganglion cells were shrunken, while in others the Nissl substance was poorly defined and the cytoplasm appeared finely granular. There was a distinct proliferation of the capsule cells. In the fat tissue about the ganglion there were focal accumulations of monocytoid cells (fig. 1). The spinal cord did not show abnormalities.

Left sixth and seventh intercostal nerves. Along the nerves many infiltrations of monocytoid cells were observed. The small blood vessels within the nerves

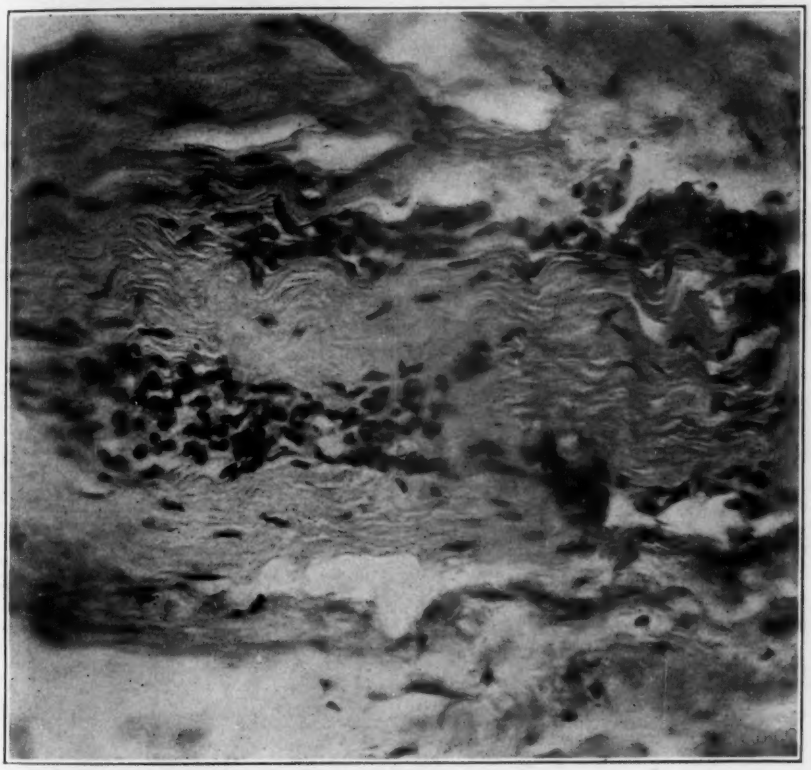

Fig. 2.—Monocytoid cells in the spinal nerve. The small blood vessels inside the nerves are filled with these cells, and there are also small interstitial perivascular accumulations of monocytoid cells.

were filled by these cells, and there were also small interstitial perivascular accumulations of monocytoid cells (fig. 2).

Lymph Nodes: Encroaching on the secondary nodules of the cortex and reducing them from small and isolated islands of lymphocytes were dense accumulations of monocytoid cells and granulocytes, which filled the lumen of the sinuses and infiltrated the trabeculae. The ratio between monocytoid cells and granulation cells was about 3 to 1. Among the latter, well developed myelocytes were most numerous. They matured to metamyelocytes and leukocytes in an orderly fashion.

Myeloblasts, with their characteristic nuclei, were rather numerous, as were also plasma cells, while megakaryocytes were scanty and nucleated red cells were conspicuously absent. There was no iron pigment, but some of the swollen reticulum cells contained erythrocytes or monocytoid cells and granulocytes (fig. 3).

Bone Marrow: The bone marrow specimen was from the femur, the cellularity of which was 93 per cent. Examination revealed:

Monocytoid cells	71.2%
Myeloblasts	0.3%
Neutrophilic myelocytes	6.1%
Neutrophilic leukocytes	0.9%
Eosinophilic myelocytes	0.1%
Mast cells	0.1%
Erythrogonias	0.3%
Erythroblasts	3.7%
Normoblasts	13.9%
Lymphocytes	0.5%
Plasma cells	1.8%
Megakaryoblasts	0.6%
Megakaryocytes	0.5%

The monocytoid cells had the tendency to form groups in which there were few other marrow cells present. However, they also appeared scattered between the myeloid elements. The megakaryocytes often showed regressive changes. The sinusoids were relatively narrow.

Spleen: The weight of the spleen was 390 Gm. and the consistency diminished. The capsule was slightly thickened and the surface smooth. On sectioning, it was revealed to be light purple-gray, soft and medullary. The follicles were prominent. The pulp was extremely cellular and closely resembled the bone marrow. The same types of cells were observed in approximately the same numerical relation. Plasma cells were more numerous than in the marrow and often contained several nuclei. The bulk of the cells occupied the cords. The sinuses were narrow and often obscured by the swelling of the endothelial cells and the large number of cells in the lumen. The trabeculae showed a moderate degree of activation of the cells, and the endothelium of the intratrabecular veins was often undermined by myeloid and monocytoid cells.

Differential Cell Count of Peripheral Blood: The differential cell count of peripheral blood was:

Monocytes	51.2%
Monoblasts	5.6%
Stem cells	3.2%
Myeloblasts	13.6%
Myelocytes	8.8%
Polymorphonuclear leukocytes	12.0%
Lymphocytes	5.6%
Normoblasts	8.0/100 white blood cells

COMMENT

Carter and Dunlop[1] defined herpes zoster as essentially acute posterior poliomyelitis due to the virus of chickenpox. Others have stated the belief that herpes zoster is due to an injury of the posterior ganglions, whether that injury be caused primarily by an acute specific virus or by any other form of trauma. It would seem that the virus is frequently

1. Carter, A. B., and Dunlop, J. B. W.: Paresis Following Herpes Zoster, Brit. M. J. **1**:234 (Feb. 15) 1941.

to be observed in the ganglions of normal persons and in some way is activated by other disease processes. According to Baird [2] the commonest "trigger factors" include the following: drugs (arsenic, lead, bismuth, mercury, iodides, gold, morphine, carbon dioxide and carbon monoxide), blood dyscrasias (especially leukemia), trauma, infectious diseases (such as influenza, encephalitis, erysipelas, tuberculosis and syphilis), vaccination, malignant tumors and Hodgkin's disease (which act either by pressure on the ganglions or by toxic effect).

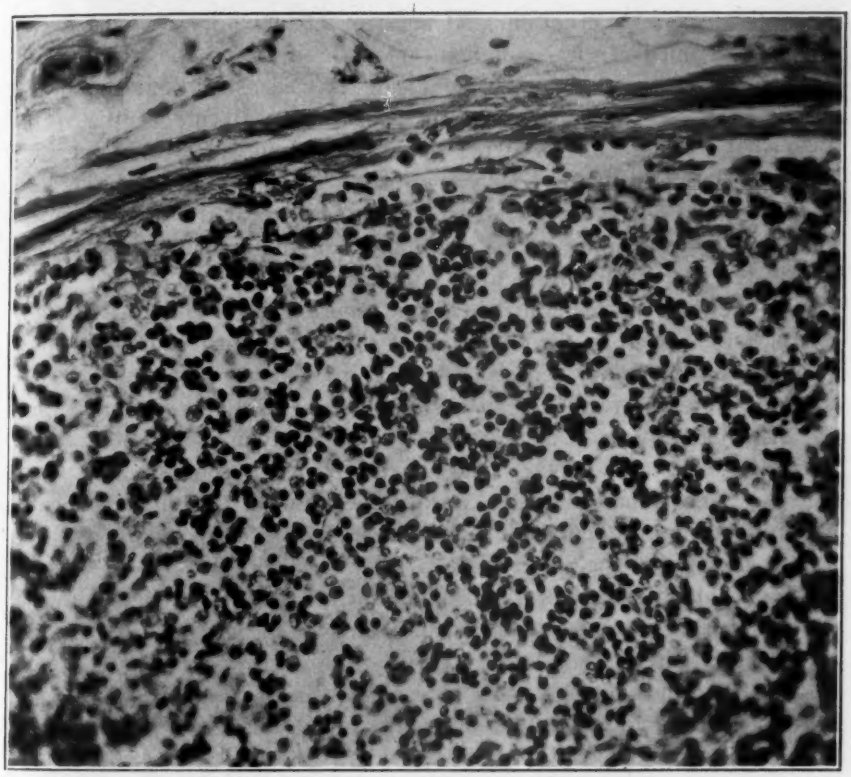

Fig. 3.—Monocytoid cells in the lymph node. Myeloblasts and plasma cells are also rather numerous.

Kumer [3] stated that leukemic infiltration can be localized in the spinal ganglion and so can produce zoster. Thus the leukemic infiltrate in the spinal ganglion can be the "trigger factor" in activating the specific virus of herpes zoster.

2. Baird, P. C., Jr.: Herpes Zoster, New England J. Med. **228**:568 (March 6) 1943.

3. Kumer, L., in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenberg, 1934, vol. 3, p. 348.

Fischl [4] was the first to report a case of generalized zoster in which the primary eruption occurred over the distribution of the fifth nerve on the right side. At autopsy both gasserian ganglions revealed periganglionic leukemic infiltration with inflammatory changes inside the ganglions, most apparent on the right side. At that time Fischl could not determine the causal relationship of the leukemic changes to the zoster.

Freund's [5] patient presented gangrenous zoster, involving the distribution of the third cervical nerve on the left side, and, in addition, a generalized vascular eruption. At autopsy inflammatory changes were seen in the third cervical ganglions on both sides and the fourth and fifth cervical ganglions on the right side as well as in their posterior roots. The second, third and fourth cervical segments of the cord showed the same changes. This relatively widespread type of inflammatory reaction of the nervous system is not unusual in ordinary herpes zoster without leukemia. A hematoma observed near the third cervical ganglion, corresponding to the distribution of the primary zoster, was considered a predisposing factor for the localization of the virus.

In the case of generalized zoster reported by Damm,[6] leukemic changes were seen in the segments of the spinal cord examined (the thoracic segments of the second and third lumbar segments). The changes were most decided in the lumbar segment, corresponding to the distribution of the primary zoster. A diffuse lymphocytic infiltration was also seen around the entrance of the posterior roots of the spinal nerves. The spinal ganglions were not examined. Damm expressed the opinion that the leukemic changes acted as a predisposing factor for the localization of the zoster virus.

In Wohlwill's [7] patient a leukemic infiltrate was observed at autopsy in both trigeminal roots, while examination of the gasserian ganglions gave negative results.

Autopsy in Scheinker's case [8] verified the clinical diagnosis and disclosed leukemic infiltration bilaterally about the nerve roots and in the spinal ganglions of the upper eight dorsal nerves. Since the herpes lesions were unilateral, the leukemic changes were considered as a pre-

4. Fischl, F.: Herpes zoster generalisatus bei Leucæmia lymphatica, Arch. f. Dermat. u. Syph. **118**:553 (Sept.) 1913.

5. Freund, H.: Zoster und Leukämie: Ein Beitrag zur Kenntnis des symptomatischen Zoster, Arch. f. Dermat. u. Syph. **154**:476 (March) 1928.

6. Damm, P.: The Etiological Connection Between Generalized Zoster, Leukemia and Chicken Pox, Ugesk. f. læger **93**:1279, 1931; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **41**:609, 1932.

7. Wohlwill, F.: Zur pathologischen Anatomie des Nervensystems beim Herpes zoster, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:171, 1924.

8. Scheinker, I.: Zur Pathogenese des Herpes zoster bei lymphatischer Leukämie, Wien. klin. Wchnschr. **50**:1065 (July 16) 1937.

disposing factor in the localization of the infectious agent of herpes and not as a direct cause of the cutaneous manifestation.

Marigonda,[9] in examining the spinal fluid, observed an increase in the number of leukocytes similar to that in the blood and therefore concluded that the spinal ganglion was affected. Spinal ganglion involvement was suspected in Carr's [10] case and in the first case of Wile and Holman,[11] but cannot be accepted because no autopsy was done.

In the case reported here, autopsy revealed leukemic monocoytic cells in the seventh left spinal ganglion and the sixth and seventh left intercostal nerves.

Cole [12] stated that the observations in patients with lymphatic leukemia do not support the view that herpes zoster may be caused by leukemic infiltration in the posterior root ganglion. It is assumed that the leukemic changes produce a "locus minoris resistantiae" where the specific zoster localizes and multiplies. Cole further suggested the possibility of a process similar to that occurring in Milian's ninth day erythema, in which the local immunity is so lowered by the leukemic infiltration that opportunity is afforded for the virus of herpes zoster to set up specific changes.

The theory that lesions in the spinal ganglions are the cause of herpes zoster has recently been proved inadequate by Wohlwill's [7] comprehensive pathologic studies of the disease. He investigated the entire peripheral nervous system in 6 cases of idiopathic and 4 cases of secondary zoster. The primary diseases in the cases of secondary zoster were gastric carcinoma, lymphosarcoma, lymphatic leukemia and syphilis, respectively. He observed that involvement of the spinal ganglions was not constant in either the idiopathic or the secondary types of herpes zoster. For example, Wohlwill observed the disease to be caused by carcinomatous infiltration of the anterior branch of an intercostal nerve, the dorsal ganglion remaining intact. In another case the posterior root was involved and in another the posterior horn of the spinal cord, the dorsal ganglions being unaffected. These observations suggested to Wohlwill that herpes zoster could be produced by involvement of any point of the afferent portion of the reflex arc. It is true, however, that the dorsal ganglion is the most frequent point of involvement.

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9. Marigonda, P.: Zoster universale emorragico-gangrenoso vericelliforme, in individuo con leucemia acuta emotico-blastica, abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **28**:280, 1928.

10. Carr, J. G.: Leukemia with Gout and Herpes Zoster, M. Clin. North America **5**:1615 (May) 1922.

11. Wile, U. J., and Holman, H. H.: Generalized Herpes Zoster Associated with Chronic Lymphatic Leukemia, Arch. Dermat. & Syph. **42**:587 (Oct.) 1940.

12. Cole, H. N., cited by Barney, R. E.: Zosteriform Leukemia Cutis, Arch. Dermat. & Syph. **37**:238 (Feb.) 1938.

Trömner and Wohlwill [13] examined the nervous system in 12 cases of leukemia. The gasserian ganglion was seen to be involved in 4 of the 9 cases in which it was studied. None of the patients had been affected wtih zoster, despite the known involvement of the ganglion.

Downey [14] divided monocytic leukemia into two types: the Schilling and the Naegeli types. He referred to the Schilling type as true monocytic leukemia, with the preponderance of monocytic cells in the bone marrow and blood stream and of reticular cell origin. The Naegeli type, on the other hand, is a monocytic phase of myelogenous leukemia, in which the myeloid cells predominate in the bone marrow despite the fact that the peripheral blood shows a majority of monocytic cells. This is of myeloblast origin. It should be noted that accurate differentiation of these forms of leukemia may be exceedingly difficult.

Naegeli expressed the opinion that the myeloblast may undergo leukemic proliferation with little or no evidence of maturation; there may be development into the myelocyte and later stages, or there may be transitions to the monoblasts with subsequent formations of older forms of the monocyte series. Bethell [15] called disease in the latter group myelomonocytic, in contradistinction to the disease in the cases of leukemia which exhibit no evidence of lymphoblastic or myeloblastic origin but rather are characterized by generalized production of cells of reticuloendothelial type. Monocytes in their several stages of development are commonly seen in the circulating blood of such patients, and frequently there occur larger "histiocytic" forms. This type of leukemia Bethell termed the histiomonocytic type.

Both specific and nonspecific cutaneous lesions have been described in association with monocytic leukemia,[16] but no case of herpes zoster in association with monocytic leukemia has been reported.

Cases of the Naegeli type of monocytic leukemia have been reported by Montgomery,[17] in which the early cutaneous manifestations simulated mycosis fungoides, and by Lynch,[16a] who reported a case of noninflammatory infiltrated lesions.

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13. Trömner, E., and Wohlwill, F.: Ueber Erkrankungen des Nervensystems insbesondere der Hirnnerven, bei Leukämie, Deutsche Ztschr. f. Nervenh. **100**: 233 (Dec.) 1927.

14. Downey, H.: Monocytic Leukemia and Leukemic Reticulo-Endotheliosis, in Bell, E. T.: Textbook of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1934.

15. Bethell, F. H.: Leukemia, Univ. Hosp. Bull., Ann Arbor **8**:65 (Aug.) 1942.

16. (*a*) Lynch, F. W.: Cutaneous Lesions Associated with Monocytic Leukemia and Reticulo-Endotheliosis, Arch. Dermat. & Syph. **34**:755 (Nov.) 1936. (*b*) Mercer, S. T.: Dermatosis of Monocytic Leukemia, ibid. **31**:615 (May) 1935. (*c*) Loveman, A. B.: Monocytic Leukemia Cutis, South. M. J. **29**:357 (April) 1936.

17. Montgomery, cited by Lynch.[16a]

Pathologically, according to Lynch, monocytic leukemia consists chiefly of mature and immature lymphocytes. These are large cells having abundant cytoplasm. The immature forms have dark nuclei, which may be reniform or bilobed; in the more mature cells, there are large or oval nuclei and the cytoplasm is frequently granular. Although the recognition of monocytes is essential for the diagnosis, it is the polymorphous infiltrate that is different from other pathologic processes. The notching of the nuclei and the large size of the cells distinguish the disease from lymphatic leukemia.

Loveman [16c] pointed out that the cellular infiltrate extends between the connective tissue fibers and does not replace them as in the more solid areas of infiltration seen in other types of leukemia. He mentioned the irregular shape of the cells and the tendency to produce pseudopods. He also emphasized the lack of practical value in application of the oxidase reaction to tissues removed from patients with monocytic leukemia.

SUMMARY

A case of herpes zoster associated with monocytic leukemia is reported for the first time.

At autopsy leukemic monocytic cells were observed in the spinal ganglion and in the intercostal nerves which were the site of the herpes zoster. The relationship of the leukemic cells in the nervous system to the herpes zoster has been commented on briefly.

30 North Michigan Avenue.

DYSTROPHIA UNGUIUM MEDIANA CANALIFORMIS

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AND
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FEW CASES of the rare disease dystrophia unguium mediana canaliformis have been reported. It was first described by Heller in 1928,[1] who gave it its name. Since then, Wucherpfennig,[2] Ledo,[3] Pardo-Castello,[4] Costa [5] and Fowle and Wiggall [6] have presented similar

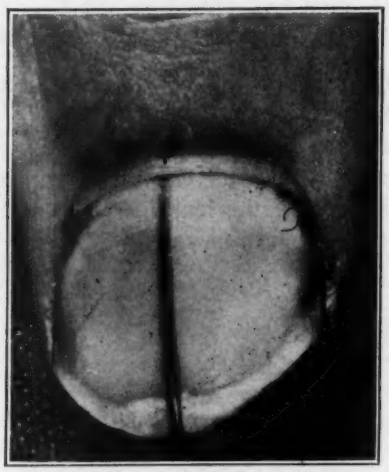

Fig. 1.—Left thumb nail showing streak.

1. Heller, J.: Zur Kasuistik seltener Nagelkrankheiten: Dystrophia unguium mediana canaliformis, Dermat. Ztschr. **51**:416 (Jan.) 1928.

2. Wucherpfennig: A Case of Dystrophia Unguium Mediana Canaliformis Heller, Dermat. Ztschr. **54**:96 (Aug.) 1928.

3. Ledo, E.: On a Case of Dystrophia Unguium Mediana Canaliformis, Ann. de dermat. et syph. **10**:765 (July) 1929.

4. Pardo-Castello, V.: Diseases of the Nails, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 96.

5. Costa, O. G.: Median Canal-Like Dystrophy of the Nails: Report of a Case, Arch. Dermat. & Syph. **49**:406 (March) 1943.

6. Fowle, L. P., and Wiggall, R. H.: Dystrophia Unguium Mediana Canaliformis: Report of a Case, Arch. Dermat. & Syph. **50**:267 (Oct.) 1944.

cases. The disease is characterized clinically by a canal which runs the length of the nail, from the root to the free edge where it becomes fissured. Thus far, the causative agent has not been determined.

Treatment has had varying results. The disease in Ledo's case responded to roentgen rays; in Pardo-Castello's and in Costa's, it did not. Fowle and Wiggall reported that the disease in their case cleared completely in a year and a half after three carious teeth were extracted.

This case is reported largely because it is a dermatologic rarity and because it demonstrates the clinical symptoms in such a classic form.

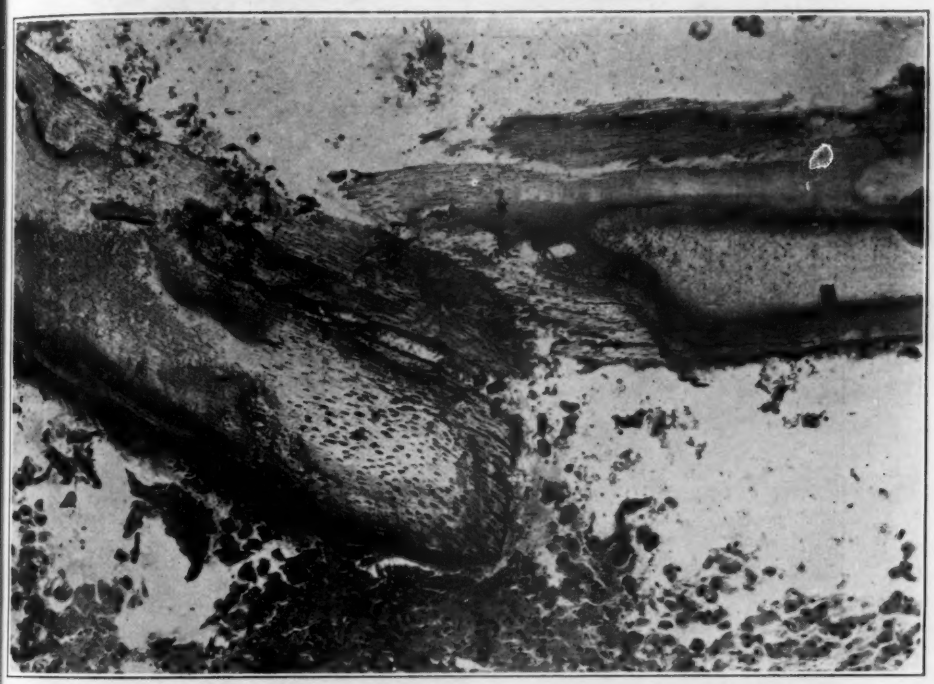

Fig. 2.—The broken nail, its two parts slightly overlapping. Apparently the canal had disintegrated in its distal parts; at least, it was not recognizable in this material.

REPORT OF A CASE

L. M., a white 12 year old girl, first noticed a streak on her left thumb nail about a year previous to examination. A history of trauma could not be elicited. Although how it first began was not clear, it would appear that the initial abnormality was a split at the free edge.

Only the one nail exhibited the streak. It extended through the entire length of the nail in the median line, from its base to the free edge where it ended in a fissure which divided the nail into two parts. Faint grayish brown at the base the streak became darker as it coursed distally, and its surface became more and more highly rounded. Its top lay on a level with the rest of the nail surface, but its margins were slightly depressed below that level. It thus resembled a hard

black cord which might have been pushed downward in the nail bed until its surface was flush with that of the nail surface in general.

The patient was not aware of the canal; it was so tiny that it admitted only a fine wire for a depth of several millimeters. The upper part of the canal contained only a minute quantity of brown debris. There had not been any perceptible change in the streak since it first appeared.

The general physical examination revealed nothing of significance. The hemogram resulted in normal observations. Scrapings of the nail were planted on Sabouraud's medium, but nothing grew except contaminants. The basal metabolic rate was within normal limits.

Fig. 3.—Details of the degenerated keratinous material and the intranuclear pigment.

The nail was allowed to grow without trimming for thirty days and protected from breaking by the use of adhesive tape. The projecting part was removed and submitted for histologic examination.

Histologic Examination.—When received in the laboratory, the sample had broken into two pieces. In order to maintain the proper relationship during sectioning, the two portions were adjusted in a slit in a piece of liver. The block of liver was thereafter fixed and sectioned. This explains the appearance of hepatic cells in the illustrations. Unfortunately, the two portions of nail slightly overlapped.

Most of the nail tissue was homogenous and hyaline, thus conforming to processes of hyperkeratosis. At the fissure, which corresponded to the position of the groove, the features of parakeratosis were observed. The persistent nuclei which characterize parakeratosis were more conspicuous in the region of the fissure and gradually tapered off laterally. The nuclei were remarkable because they were crowded with granules of melanin; in fact, they might well have escaped observation were it not for the pigment; the amount of chromatin was excessively small. It was not possible to establish the canal. Numerous bacteria were scattered over both sides of the nail and in the region of fracture.

COMMENT

Unfortunately, a sample of tissue could not be obtained farther up on the nail, where the canal still maintained its form; this might have given information as to the situation leading to its formation. It would also be informative to learn what the conditions were at the base of the nail under the nail fold, i. e., at the point of origin of the malformation. However, a definite lesion could not be recognized there, even when the nail fold was pushed far back.

We were therefore limited to two new histologic observations, namely, that processes of parakeratosis were concerned in the streak and that the pigmentation was intranuclear. These support the thesis that a focus of pigmentary dystrophy (dyskeratotic) lay in the nail bed, under the nail fold; this elongated to produce a linear malformation as the nail grew. This eliminated an alternative thesis, namely, that the blackness might be due to degenerative changes in ancient keratin. The central portion of this soft parakeratotic material degenerated and disintegrated, resulting in the canal.

In the absence of definite information as to the nature of the original lesion it is hazardous to conclude that the disease is an etiologic entity. It could be an intradermal nevus or simple pigmentary dyskeratosis and parakeratosis, but the end result in all cases would have to be parakeratosis (to account for softening and the canal formation) with hyperpigmentation. In the sections in our case there were simply the end results of the fundamental processes.

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MYOEPITHELIAL SWEAT GLAND TUMOR: MYOEPITHELIOMA

Report of Three Cases with a Review of the Literature

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ECCRINE and apocrine sweat glands possess tubular lumens lined by two layers of cells. In their secretory portion the inner layer is composed of secretory cells and the outer layer of myoepithelial cells. Tumors affecting the secretory portion of sweat glands, therefore, contain, as a rule, both secretory and myoepithelial cells. In most of these tumors the myoepithelial cells are far less numerous than the secretory cells. There exists, however, a group of benign sweat gland tumors in which the myoepithelial cells represent the majority of tumor elements. These tumors present histologic characteristics which make their recognition as a separate type of sweat gland tumor desirable. The term myoepithelioma is suggested as designation for these tumors.

Descriptions of 12 cases of tumor of this type were found in the literature. Three additional cases were observed at the Massachusetts General Hospital. These 15 cases of tumor will be described in this paper. Their description is preceded by comments on the occurrence of myoepithelial cells in sweat gland tumors in general.

OCCURRENCE OF MYOEPITHELIAL CELLS IN SWEAT GLAND TUMORS

Carcinoma of Sweat Glands.—Darier,[1] Grynfeltt and Aimes (case 2),[2] Blavet di Briga,[3] Loos[4] and Sheldon (case 3)[5] have described the pres-

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From the Departments of Dermatology and Pathology, Massachusetts General Hospital.

1. Darier, J.: Contribution à l'étude de l'épithéliome des glandes sudoripares, Arch. de méd. expér. et d'anat. path. **1**:115 and 267, 1889.

2. Grynfeltt, E., and Aimes, A.: Etude histo-pathologique de deux tumeurs des glandes sudoripares, Bull. Assoc. franç. p. l'étude du cancer **11**:91, 1922.

3. Blavet di Briga, C.: Adenocarcinoma papillifero a tipo apocrino della mammella, Arch. per le sc. med. **49**:385, 1927.

4. Loos, H. O.: Die Carcinome der Anhangsgebilde der Haut, Arch. f. Dermat. u. Syph. **174**:465, 1936.

5. Sheldon, W. H.: The Myoepithelium in Sweat Gland Tumors, Arch. Path. **31**:326 (March) 1941.

ence of myoepithelial cells in sweat gland carcinomas. In the cases reported by Darier, Blavet di Briga and Loos, the myoepithelial cells did not assume particular importance. However, in those reported by Grynfeltt and Aimes and by Sheldon the myoepithelial cells predominated as the main element in the tumor formation.

Hidradenoma Papilliferum (Vulvae).—In many hidradenomas the glandlike formations of secretory cells are surrounded by myoepithelial cells. Usually, the myoepithelial cells are arranged in a single layer. Occasionally, however, they show proliferation into the adjoining stroma, as observed by Ruge,[6] Schiffmann,[7] Blau,[8] McDonald[9] and Sheldon (case 2).[5] In Sheldon's case the proliferation of the myoepithelial cells was of such degree that their numbers equaled that of the secretory cells. McDonald, in a report of 30 cases, expressed the opinion that all hidradenomas were carcinomas, because of the presence of "carcinomatous infiltrative cells." His photomicrographs suggest, however, that the cells thus referred to are myoepithelial cells. Consequently, there seems to be no reason to regard these tumors as carcinomas.

Syringocystadenoma Papilliferum (Nevus Syringocystadenomatosus Papilliferus).—Two types of cells are regularly present in this tumor: an inner layer of high cylindric cells, showing active secretion, and an outer layer of small cells, usually of cubic but occasionally of spindle shape. The differentiation of the cells of the peripheral layer toward spindle-shaped myoepithelial cells is rarely pronounced, because the tumor is an adenoma more of the ductal than of the secretory portion of apocrine sweat glands.

Syringoma.—This tumor too shows differentiation mainly toward apocrine sweat ducts. For this reason, myoepithelial cells are usually absent. Occasionally, however, some are present surrounding actively secreting cells, as in the cases of syringoma described by Weidman and Besancon[10] and by Masure, Pirot and Le Méhauté.[11]

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6. Ruge, H.: Ueber Vulvaaffektionen und ihre gynäkologische Bedeutung (Schweissdrüsenkarzinome), Ztschr. f. Geburtsh. u. Gynäk. **56**:307, 1905.

7. Schiffmann, J.: Schweissdrüsenadenocancroid der Vulva, Zentralbl. f. Gynäk. **44**:59, 1920.

8. Blau, A.: Hidradenoma vulvae, Ztschr. f. Geburtsh. u. Gynäk. **93**:341. 1928.

9. McDonald, J. R.: Apocrine Sweat Gland Carcinoma of the Vulva, Am. J. Clin. Path. **11**:890, 1941.

10. Weidman, F. D., and Besancon, J. H.: Histologic Differences in a "Syringoma" of the Face and Shoulder: Employment of Wax Reconstruction, Arch. Dermat. & Syph. **21**:279 (Feb.) 1930.

11. Masure; Pirot, R., and Le Méhauté: Hidradénomes éruptifs ou syringocystadénomes, Bull. Soc. franç. de dermat. et de syph. **43**:1050, 1936.

Cylindroma.—Many observers [12] have noted the presence of two types of cells in lesions of cylindroma. Cells with large oval light-staining nuclei lie in the center of epithelial cell islands, while cells with small round dark-staining nuclei are present at the periphery of the epithelial cell masses and, also, scattered between the cells of the first type. No attempt has been made by any of these authors to explain the nature of the two types of cells. In a separate communication [13] I give reasons for my belief that the cells of the first type are cells differentiating toward secretory cells and those of the second type cells differentiating toward myoepithelial cells of apocrine sweat glands. The hyalin which is present around the cell islands and, frequently, also within the islands appears to be produced by the myoepithelial cells, since it is always observed in contact with the myoepithelial cells.

Adenoid Basal Cell Epithelioma.—As discussed in a separate communication,[13] I regard adenoid basal cell epithelioma as a tumor originating from the primary epithelial germ and showing beginning differentiation toward apocrine sweat glands. Occasionally, differentiation into two types of cells, secretory and myoepithelial cells, can be observed. Some of the more highly differentiated adenoid basal cell epitheliomas resemble myoepitheliomas, but differ from them by the lack of sharp demarcation and the presence of fewer and less differentiated lumens

CASES OF MYOEPITHELIOMA DESCRIBED IN THE LITERATURE

Reports of 12 cases to which the diagnosis of myoepithelioma may be applied were found.

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12. Frieboes, W.: Beitrag zur Klinik und Histopathologie der gutartigen Hautepitheliome, Berlin, S. Karger, 1912. Watanabe, J.: Ueber das Cylindrom und das Epithelioma adenoides cysticum (Ergebnisse der Untersuchung eines Falles Spieglerscher Tumoren), Arch. f. Dermat. u. Syph. **140**:208, 1922. Biberstein, H.: Epithelioma adenoides cysticum im Gesicht und Cylindrome am behaarten Kopf, ibid. **142**:428, 1923. Balog, P.: Beitrag zur Frage des Schweissdrüsennävus, Dermat. Wchnschr. **82**:841, 1926. Wiedemann, A.: Weitere Beiträge zur Kenntnis der sogenannten Zylindrome der Kopfhaut, Arch. f. Dermat. u. Syph. **159**:180, 1930. Glasunow, M.: Ueber die gutartigen Geschwülste der Schweissdrüsen, Ztschr. f. Krebsforsch. **33**:431, 1931. Kogoj, F.: Ueber das Verhalten des Hyalins in Cylindromen, Arch. f. Dermat. u. Syph. **166**:515, 1932. Stillians, A. W.: Nevo-Epithelioma Adenoides (Cylindroma) of the Scalp, Arch. Dermat. & Syph. **27**:481 (March) 1933. Schlammadinger, J.: Cylindrom und Trichoepithelioma papulosum multiplex, Arch. f. Dermat. u. Syph. **171**:526, 1935. Zakon, S. J.: Naevo-Epithelioma Adenoides (Cylindroma) of the Scalp, Arch. Dermat. & Syph. **40**:945 (Dec.) 1939.

13. Lever, W. F.: Pathogenesis of the Benign Tumors of the Cutaneous Appendages and of Basal Cell Epithelioma, Arch. Dermat. & Syph., to be published.

Grynfeltt and Aimes (case 1)[2] described a tumor located on the forehead of a woman aged 42. In the course of twelve years the tumor had grown to the size of half a walnut. The tumor was covered by intact erythematous skin and was movable with the skin. Histologic examination revealed a well circumscribed, but not encapsulated, tumor, not connected with the epidermis. The tumor was composed of lobular masses in the center and winding cords at the periphery. Both types of formations were surrounded more or less completely by hyaline membranes. Two types of cells composed the tumor. Secretory cells ("cellules cuticulaires") lay in groups, frequently arranged around small lumens. They possessed pale-staining round or oval nuclei and a granulated strongly eosinophilic cytoplasm. Myoepithelial cells ("cellules basilaires"), which greatly outnumbered the secretory cells, were arranged in an irregular fashion around the groups of secretory cells. They had deeply staining nuclei and a delicate cytoplasm. In the larger cell masses these cells often were elongated, closely spaced and arranged in strands and whorls. The authors stated that in these areas they resembled smooth muscle cells. They regarded the tumor as benign and called it "adéno-épithéliome sudorifère."

Sutton [14] described the case of a woman, aged 45, who presented on the right side of her neck numerous nodular lesions varying in size from 2 to 10 mm. Most of them had been present since childhood, but some had appeared in recent years. They had gradually grown in size. The lesions were movable with the skin. The overlying skin was normal. Histologic examination of a lesion revealed a fairly well encapsulated tumor, in which the cellular proliferation seemed to take the form of cylinders, branching, massed, interlaced and of varying diameter depending on the degree of proliferation of the peripheral layer of a tubule of two layers. The cells of the outer layer formed the mass of the neoplasm. Their cytoplasm was scanty and their nuclei oval and deeply basophilic. The cells lining the tubules in a single layer were of a different appearance. Their cytoplasm was eosinophilic and their nuclei pale. The author stated that the peripheral cells resembled lymphoid cells and the cells of the inner cell layer renal tubule cells. He regarded the peripheral cells as sheath cells and the inner cells as secretory cells of sweat glands. Several large cysts lined by secretory cells were present in the tumor. Sutton suggested as designation for this tumor sheath cell syringocystadenoma.

Sheldon (case 1)[5] observed in a girl, 10 years of age, a bean-sized firm nodule within the thickness of the right cheek. The lesion had first been noted two months previously. The tumor was surrounded

14. Sutton, R. L., Jr.: A Rare Sweat Gland Tumor: Syringocystadenoma Nodularis, Arch. Dermat. & Syph. **30**:195 (Aug.) 1934.

by a fairly thick connective tissue capsule which included several essentially normal eccrine sweat glands. Direct continuity between these glands and the tumor was observed in several instances. The tumor was composed of epithelial cells arranged in solid cords, in convoluted ductlike and glandlike formations and in dense masses without particular arrangement. Two types of cells were present. The cells of the first type, which in Sheldon's opinion were myoepithelial cells, were elongated and spindle shaped and had deeply basophilic rod-shaped nuclei. Longitudinal fibrils were seen in their cytoplasm. They represented the vast majority of tumor elements. They composed the solid structures and were arranged, frequently, in several layers at the periphery of the ductlike and glandlike structures. The cells of the second type had oval or round nuclei and a granular eosinophilic cytoplasm. They lined the lumens of the ductlike and glandlike structures. Some of the lumens contained moderate amounts of granular pinkish-staining material, occasionally intermingled with desquamated epithelial cells. Sheldon regarded the tumor as a benign spiradenoma with proliferation mainly of the myoepithelial cells.

Balog [15] described a tumor which had been present for three months on the thigh of a girl aged 19, was as large as a hazelnut and was movable with the skin. The tumor was encapsulated and composed of numerous bandlike and alveolar cell masses in which narrow lumens were present. The lumens were lined by a single row of large cubic or slightly flattened epithelial cells which had large oval or round nuclei and an intensely eosinophilic cytoplasm. Surrounding these glandular ducts were one or, more often, several layers of epithelial cells which were small and round or angular and contained deeply basophilic nuclei. Balog, as Sutton had done, compared these cells to lymphocytes. He expressed the belief that the tumor had developed from embryonic sweat ducts, and he regarded the large cells as those of the inner row and the small cells as those of the outer row of sweat ducts. The smaller cells outnumbered the larger cells by far. The stroma of the tumor consisted almost entirely of dilated lymph spaces. His designation for the tumor was adenoma hidradenoides parenchymatosa cum lymphostasi.

Several tumors described in the literature as mixed tumors of the skin may be classified as myoepitheliomas. They differ from the previously described tumors only by the higher degree of hyalinization of the connective tissue stroma. The presence of hyaline connective tissue tends to give these tumors the appearance of mixed tumors, similar to those of the salivary glands. A review of the cases in which

15. Balog, P.: Beitrag zur Frage der Schweissdrüsenadenome-, Adenoma hydradenoides parenchymatosa cum lymphostasi, Acta dermat.-venereol. **22**:187, 1941.

the growths were reported as mixed tumors of the skin reveals that at least eight,[16] possibly more, can be regarded as sweat gland tumors with preponderant proliferation of the myoepithelial cells.

In Kreibig's first case [16a] the tumor was located over the right tibia of a 38 year old man, was of six years' duration and was the size of a small apple. Embedded in a ground substance which had the appearance of hyaline cartilage, there were strands of cells with small spindle-shaped nuclei as well as glandular formations composed of two rows of cells, an outer row of spindle-shaped cells and an inner row of high cylindric cells. In Kreibig's second case, concerning a 30 year old man, the tumor had been present on the left forearm for three years and had attained the size of a hazelnut. The histologic appearance was similar to that of the tumor in Kreibig's first case.

Delaney [16b] described a tumor located on the scalp of a 59 year old patient, which had been present for fifteen years and measured 15 mm. in its largest diameter. The tumor showed intercommunicating and free tuboalveolar structures in which the lumens were lined by cells which were round to oval in shape and contained an acidophilic cytoplasm. They resembled the cells lining the lumens of sweat glands. The cells of the outer layer of the tuboalveolar structures had intracellular fibrils and resembled myoepithelial cells. In many places there was proliferation of either the acidophilic or the myoepithelial cells into the adjoining stroma. The stroma was homogeneous, stained intensely red with mucicarmine and in some areas resembled cartilage. Delaney expressed the belief that the invasion of the epithelial cells had caused the transformation of the collagenic connective tissue stroma into a pseudocartilagenous matrix.

Geschickter and Koehler [16c] described the histologic appearance of a tumor which had been present for fifty years on the dorsum of the wrist of a patient aged 77. It showed small compressed basal cells surrounding small cystic or acinar spaces filled with coagulated amorphous material. In addition, there were strands of similar cells compressed by a faintly staining hyaline or mucoid substance. The photomicrograph of the tumor suggests that the "compressed basal cells" were myoepithelial cells.

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16. (*a*) Kreibig, W.: Ueber ungewöhnlich gelegene Geschwülste vom Bau der Speicheldrüsenmischtumoren, Frankfurt. Ztschr. f. Path. **42**:281, 1931. (*b*) Delaney, P. A.: Mixed Tumor of the Scalp, Arch. Path. **12**:145 (July) 1931. (*c*) Geschickter, C. F., and Koehler, H. P.: Ectodermal Tumors of the Skin, Am. J. Cancer **23**:804, 1935. (*d*) Vidari, E.: Zur Kenntnis der Gewächse vom Bau der Speicheldrüsenmischtumoren ungewöhnlichen Sitzes, Frankfurt. Ztschr. f. Path. **48**:209, 1935. (*e*) Morehead, R. P.: Mixed Tumors of the Skin: Report of Cases, with a Consideration of the Histogenesis of Mixed Tumors of Organs Derived from the Ectoderm, Arch. Path. **40**:107 (Aug.) 1945.

In Vidari's case [16d] three small tumors had been present since early youth on the left calf of a man aged 58. Two were as large as peas and one as large as a cherry. The histologic examination of one lesion revealed a connective tissue capsule around the tumor. The stroma was of hyaline appearance. Embedded in this stroma were epithelial tubules and strands. The tubules had branching lumens filled with cellular detritus and were lined by two rows of epithelial cells, an inner row of high cylindric cells and an outer row of flat cells. The strands were comprised of small round or spindle-shaped cells. The photomicrographs suggest that the cells composing the outer row of the tubules and those composing the strands were myoepithelial cells.

Morehead (cases 1, 2 and 4)[16e] described three mixed tumors of the skin in which the proliferation of myoepithelial cells was an important component. The first tumor, from the breast of a Negro woman aged 64, had been present for ten years and measured 1.5 cm. in diameter. The second tumor had been present on the nose of a 69 year old Negro for twenty years and measured 3 cm. in diameter. The histologic appearance of the two tumors was essentially the same. They were encapsulated and composed of columns, islands and tuboalveolar collections of epithelial cells. The cells at the periphery of the epithelial collections were myoepithelial cells showing proliferation into the stroma. Both tumors contained cystic spaces lined by a double layer of epithelial cells. The stroma had in places a hyaline, myxomatous or chondromatous appearance.

The third tumor (case 4) had been present for more than ten years on the ear of a 53 year old woman. It measured 1 cm. in diameter. The tumor consisted of "cylindromatous" hyalinized bands of collagen which communicated freely with one another. Between the bundles of collagen were numerous epithelial cells. In addition, there were alveolar structures lined by two layers of cells, an inner layer of tall cuboidal epithelial cells and an outer layer of myoepithelial cells. The photomicrographs suggest that the epithelial cells located between the bundles of collagen were also mostly myoepithelial cells.

REPORT OF CASES

CASE 1.—A woman, 54 years of age, had had a small nodule on her abdomen for more than ten years. The lesion was movable with the skin. The overlying skin was slightly reddened but otherwise normal. The nodule was excised.

Grossly, the specimen showed, embedded in the corium, a firm pale yellow nodule, measuring 8 by 8 by 6 mm. in diameter.

On histologic examination the epidermis appeared slightly atrophic. The tumor was entirely surrounded by a connective tissue capsule and was composed of epithelial cells arranged in most areas as intertwining cords, but in some areas as irregular masses (fig. 1). Islands of connective tissue were interspersed throughout the tumor. The connective tissue had a hyaline appearance and

possessed only few cells. Two types of epithelial cells composed the tumor (fig. 2). The cells of the first type showed large pale nuclei of oval or round shape and had a homogeneous eosinophilic cytoplasm. They were arranged in small groups, which either were located in the center of the epithelial cords or were irregularly distributed through the cell masses. Frequently the cells were grouped in a single layer around a small lumen. Some showed evidence of active secretion, in so far as part of their cytoplasm protruded into the lumen. The cells of the second type had small deeply basophilic nuclei of angular and elongated shape.

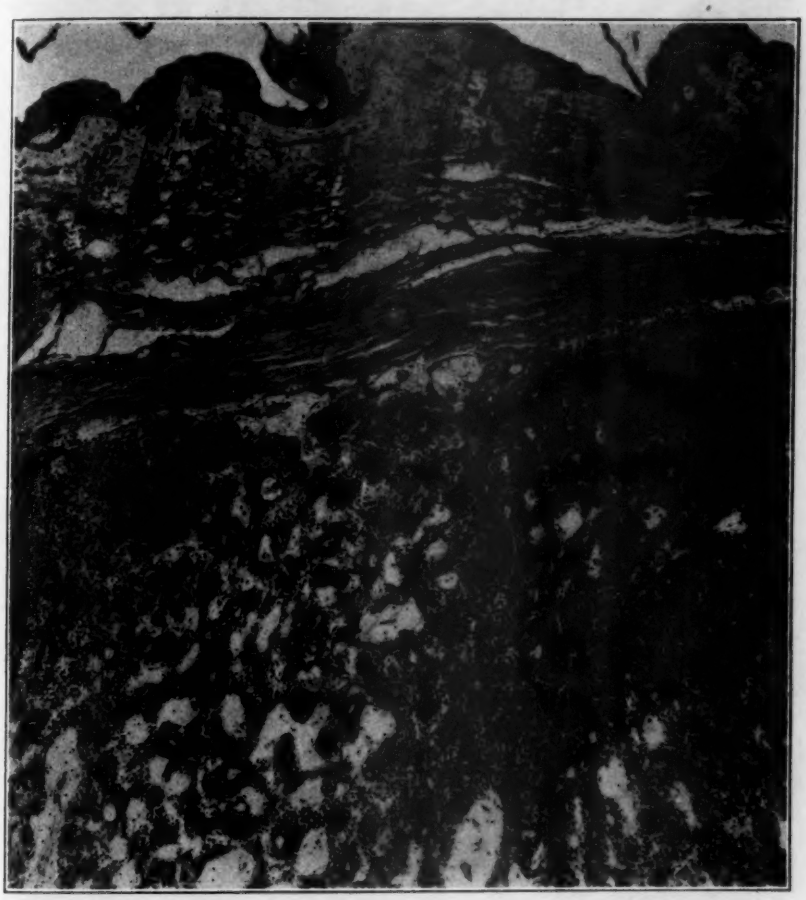

Fig. 1 (case 1).—The tumor is encapsulated. At the left the tumor is composed of bands and at the right of lobular masses. Numerous small glandular lumens are present in the tumor.

Their cytoplasm also differed from that of the first type of cell in that it stained either faintly basophilic or not at all. The cytoplasm of some contained fibrils. The cells of the second type were located around the groups of cells of the first type. In the epithelial cords they formed the outer layers, and in the cell masses they filled the spaces between the groups of cells of the first type. The cells of the second type greatly outnumbered those of the first type.

It is my belief that the cells of the first type were secretory cells, because many of them were arranged around lumens and showed active secretion into the lumens. The cells of the second type represented myoepithelial cells, because of their arrangement around the groups of secretory cells, the elongated shape of their nuclei and the presence of fibrils in their cytoplasm.

Fig. 2 (case 1).—Higher magnification shows the two types of epithelial cells. The secretory cells, which possess large round pale nuclei and an eosinophilic cytoplasm, lie in small groups and frequently are arranged around lumens. The myoepithelial cells, which possess small deeply basophilic nuclei are arranged peripheral to the small groups of secretory cells. Fibrils are present in the cytoplasm of some of the myoepithelial cells.

Case 2.—A woman, 27 years of age, first noticed a small nodule on her right shin eight years before admission. The lesion had shown slight increase in size during the last year. The nodule, 1.5 cm. in diameter, was covered by normal skin and was movable with the skin. The lesion was excised.

The specimen showed, embedded in the corium, a homogeneous grayish white circumscribed mass, measuring 1.3 by 1.3 by 1.0 cm. in diameter.

The histologic appearance of the tumor resembled in its essential features that of case 1. The tumor was encapsulated. Its epithelial cells were all arranged in intertwining strands. Large solid cell masses, however, as observed in the first tumor, were absent. Myoepithelial cells greatly outnumbered the secretory cells. Glandular lumens were fewer than in the previous tumor (fig. 3). The border of the epithelial cell strands was not always sharply demarcated, and myoepithelial cells were seen proliferating into the stroma.

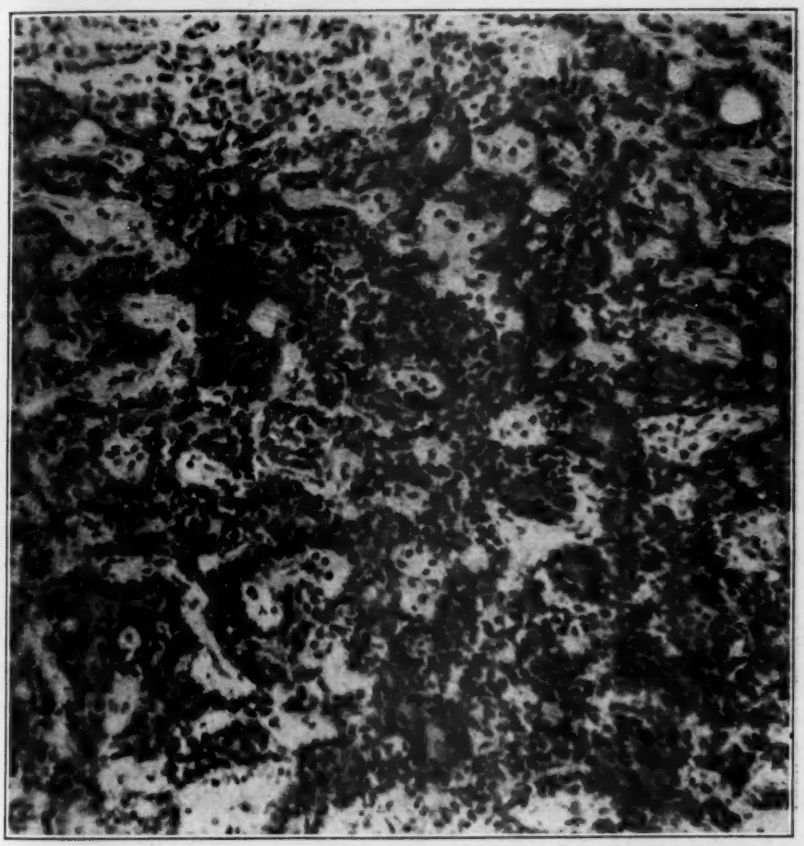

Fig. 3 (case 2).—The tumor is composed of convoluted epithelial bands, with secretory cells in the center and myoepithelial cells at the periphery. Three small glandular lumens are shown. The connective tissue has a hyaline appearance.

The stroma of the tumor was eosinophilic and had a hyaline appearance. Near the periphery of the tumor the stroma exceeded in mass the epithelium. Here, secretory cells were absent and only few myoepithelial cells, lying either singly or arranged in narrow cords, were seen embedded in the hyalinized stroma. Only their nuclei were recognizable, their cytoplasm having merged indistinguishably with the hyaline stroma.

CASE 3.—A woman, 34 years of age, presented on the right side of her neck a nodule, which had first been noted ten months previously. The lesion measured 1 cm. in diameter, was firm to the touch and was movable with the skin. It was excised.

Gross examination revealed a sharply demarcated tumor measuring 7 mm. in diameter, embedded in the corium and without connections with the epidermis.

Histologic examination revealed a connective tissue capsule around the tumor. The tumor was composed of lobules which were separated by strands of connective tissue. Some of the lobules contained large elongated branching lumens (fig. 4), and others contained only small lumens (fig. 5). The lumens were

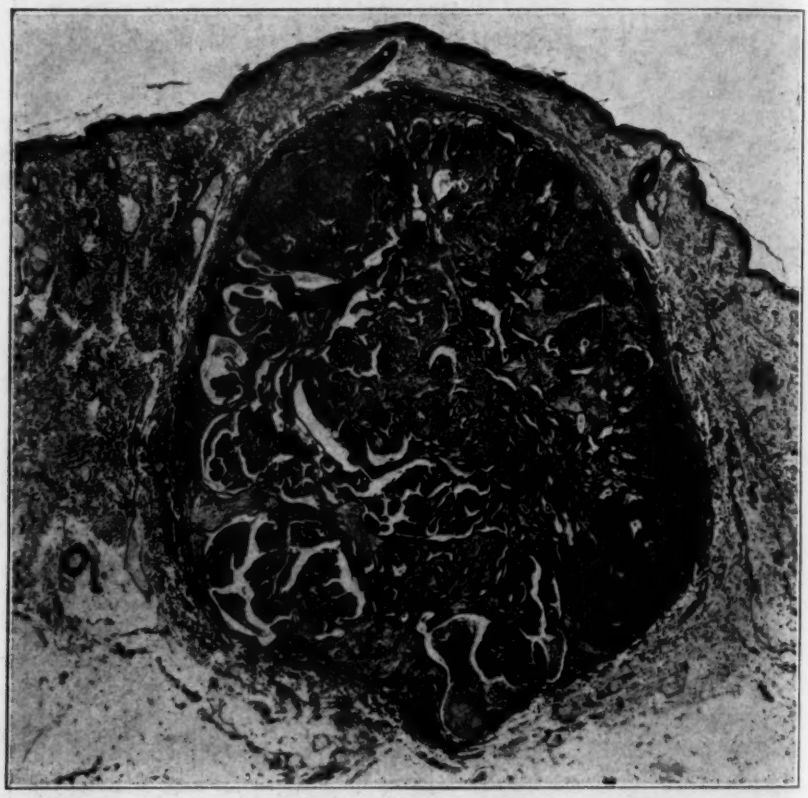

Fig. 4 (case 3).—The tumor is encapsulated and composed of lobules which are separated by strands of connective tissue. Some lobules contain large elongated branching lumens, and others contain only small lumens.

lined by a single row of secretory cells, which were large and cuboidal. They possessed an eosinophilic cytoplasm and large round or oval vesicular nuclei. Many of these cells displayed evidence of active secretion, showing projections of their cytoplasm into the lumen (fig. 6). Most lumens contained cellular detritus. The cells composing the lobules differed in appearance from those lining the lumens. Their cytoplasm was less eosinophilic, lacked a definite border and frequently contained long fibrils. Their nuclei were elongated, often spindle shaped, and were smaller and stained darker than the nuclei of the secretory cells.

In most areas these cells lay in irregular fashion; occasionally, they were arranged in strands with fibrils stretching from one nucleus to the next. They were regarded as myoepithelial cells. At the margin of some of the lobules the fibrils of the myoepithelial cells were thick, strongly eosinophilic and homogeneous, forming an encapsulating membrane of hyaline appearance.

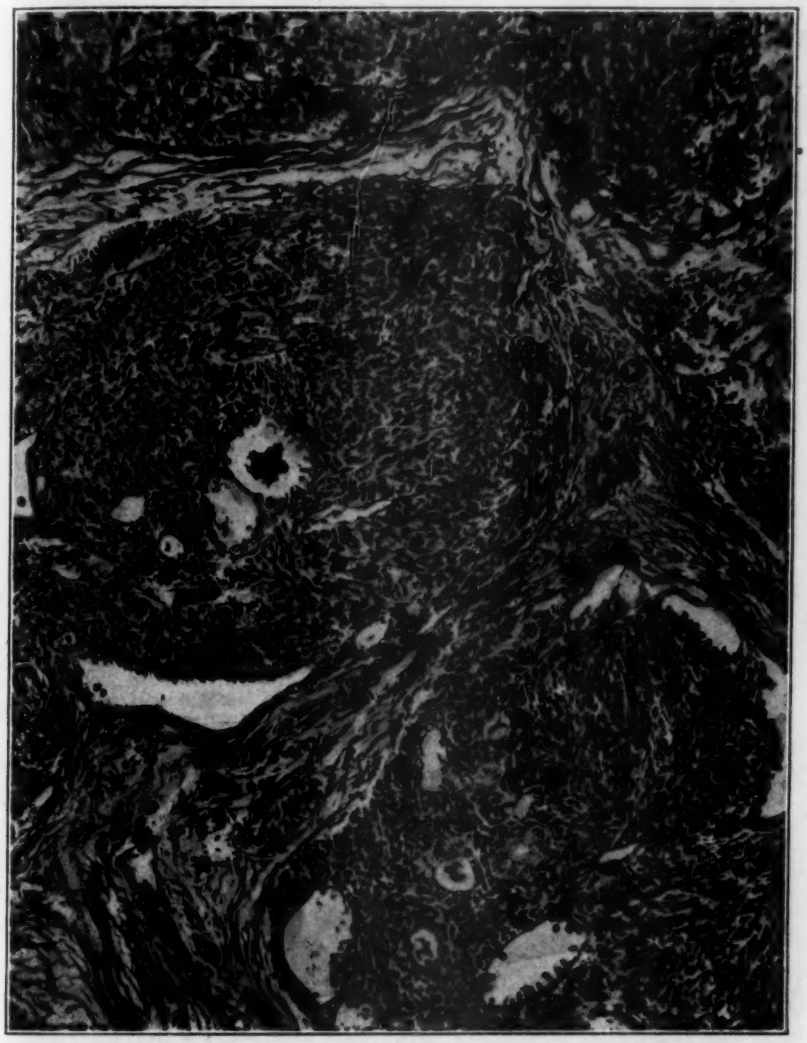

Fig. 5 (case 3).—Higher magnification shows small lumens inside the lobules.

COMMENT

Clinical Appearance.—In all 15 cases the tumors presented themselves as well demarcated intracutaneous nodules which were movable with the skin. The overlying skin was intact and, in most cases, slightly reddened. The tumors were single in 13 and multiple in

2 cases. They had first appeared in childhood, adolescence or middle age. Most of them had been present for many years and were either slowly growing or stationary. Nine patients were female and 6 male. The location of the lesions was on the face in 3, the scalp in 1, the ear in 1, the neck in 2, the trunk in 2 and the extremities in 6 patients. Their size, at the time of excision, varied from 0.2 to approximately 5 cm. The average size was approximately 1 cm. in diameter.

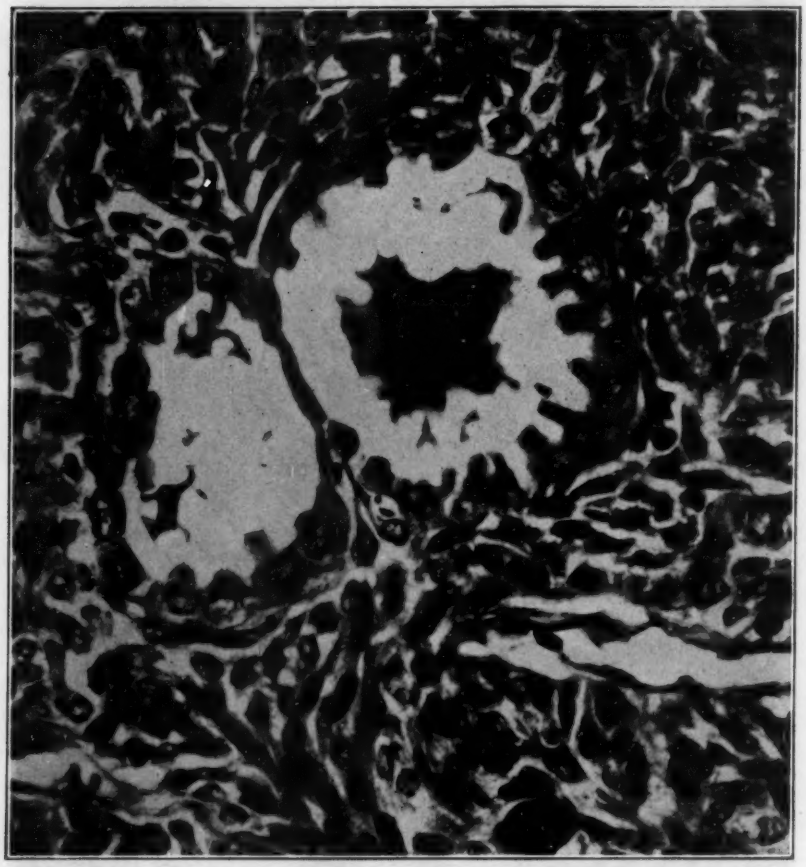

Fig. 6 (case 3).—High magnification shows the two types of cells. The majority of cells are myoepithelial cells, with deeply staining frequently spindle-shaped nuclei. Many of them contain fibrils in their cytoplasm. The lumens are lined by a single layer of secretory cells, which show active secretion.

Histologic Appearance.—The tumors were well circumscribed and usually surrounded by a connective tissue capsule. The epithelial cells were arranged in tubules, intertwining cords or lobular masses. In most tumors all three types of arrangement were seen. Two types of cells, secretory and myoepithelial cells, composed the tumors. The

latter cells represented the majority of tumor elements. The arrangement of the two types of cells followed in all tumors the same pattern, namely, myoepithelial cells surrounding groups of secretory cells.

The secretory cells showed an eosinophilic cytoplasm and large pale nuclei. In areas of bandlike arrangement they lay in the center of the bands. In areas of lobular arrangement they lay in groups. There was either a single group in the center, if the lobule was small, or several groups scattered through the lobule, if the lobule was large. The bands or groups of secretory cells were either solid or contained a central lumen. Wherever there were lumens, the secretory cells were arranged in a single layer around the lumen.

The myoepithelial cells possessed small deeply staining elongated often spindle-shaped nuclei and a poorly staining cytoplasm in which fibrils could be occasionally recognized. These cells were arranged, in the epithelial bands, peripheral to the centrally located secretory cells in one or, more often, in several layers. In the lobules with only one, centrally located, group of secretory cells, they were arranged around this group. In lobules with several groups of secretory cells they filled the spaces between these groups.

The amount of stroma in the tumors varied. In many it constituted a considerable proportion, had a hyaline appearance and even showed, in places, a cartilaginous or mucoid transformation. Such tumors greatly resembled the so-called mixed tumors of the salivary glands. In cases 2 and 3 the impression was gained that the hyaline ground substance was a product of the myoepithelial cells.

The question arises whether the reported cases of myoepithelioma were of apocrine or eccrine origin. Most authors did not discuss this question. Sheldon regarded his tumor as of eccrine origin, because of the presence of eccrine sweat glands in the connective tissue capsule around the tumor. In only one of the tumors, namely, in case 3, was differentiation of the glandular lumens sufficiently advanced so that there was no question about their being apocrine lumens. However, the fact that some of the secretory cells in Sutton's, Sheldon's and Vidari's cases and in cases 1 and 2 showed evidence of active secretion, and the fact that in most cases the secretory cells were eosinophilic would be in favor of an apocrine origin for all cases of myoepithelioma. It is possible, however, that some are of eccrine and others of apocrine origin.

Relation of Myoepithelioma to Other Apocrine Sweat Gland Tumors.—In a separate communication [13] concerning tumors arising from the primary epithelial germ I present a classification of apocrine gland tumors. I express the opinion that, while apocrine carcinomas usually arise from mature apocrine gland cells, benign apocrine gland tumors

arise from primary epithelial germ cells which, prior to the onset of neoplasia, had attained a certain degree of differentiation toward apocrine gland cells. The benign apocrine tumors are divided, according to the degree of differentiation, into organic hamartomas (apocrine nevi), organoid hamartomas (apocrine adenomas), suborganoid hamartomas (apocrine epitheliomas) and nonorganic hamartomas (adenoid basal cell epitheliomas). Two types of apocrine adenoma are recognized, namely, hidradenoma papilliferum (vulvae), in which differentiation is directed mainly toward the secretory portion, and syringocystadenoma papilliferum (nevus syringocystadenomatosus papilliferus), in which differentiation is directed mainly toward the ductal portion of apocrine glands. The apocrine epitheliomas are divided into three types, namely, syringoma, with differentiation mainly toward ductal cells, cylindroma, with differentiation mainly toward secretory cells, and myoepithelioma, with differentiation mainly toward myoepithelial cells.

The recognition of myoepithelioma as a separate type of benign sweat gland tumor appears justified on the basis of distinct histologic characteristics: (1) sharp demarcation from the surrounding tissue, (2) arrangement of the cells in tubules, bands and lobules, (3) presence of two types of cells: myoepithelial and secretory cells, with predominance of myoepithelial cells, (4) arrangement of the myoepithelial cells peripheral to groups of secretory cells and (5) presence of usually small lumens lined by secretory cells. The allocation of myoepithelioma into the group of apocrine epitheliomas is suggested because they are too highly differentiated to be regarded as basal cell epitheliomas, but not highly enough to be classified as adenomas.

SUMMARY

Myoepithelial cells are frequently present in tumors affecting the secretory portion of sweat glands. They may occur in sweat gland carcinoma, hidradenoma papilliferum (vulvae), syringocystadenoma papilliferum, syringoma, cylindroma and adenoid basal cell epithelioma.

In addition, there exists a type of benign sweat gland tumor in which myoepithelial cells represent the majority of tumor elements. These tumors, because of their characteristic histologic appearance, which differs from that of all other sweat gland tumors, deserve recognition as a distinct entity. Twelve such tumors were found described in the literature. Three additional tumors were observed at the Massachusetts General Hospital. The designation myoepithelioma is suggested for these tumors.

Clinically, myoepitheliomas are usually single, but occasionally multiple, well circumscribed intracutaneous tumors of slow growth.

Histologic examination reveals the epithelial cells arranged in tubules, intertwining bands or lobular masses. Two types of cells are present, secretory and myoepithelial cells. The latter predominate. The secretory cells lie in small groups and frequently are arranged around lumens. The myoepithelial cells are located, in the epithelial bands, at the periphery and, in the lobules, around and between the groups of secretory cells. Some of the tumors possess a considerable amount of stroma of hyaline appearance, with areas of mucoid or cartilaginous transformation. They thus resemble the mixed tumors of salivary glands. Several tumors described in the literature as mixed tumors of the skin can be classified as myoepitheliomas.

Most, if not all, myoepitheliomas may be regarded as apocrine rather than eccrine tumors, because of the eosinophilic staining of the secretory cells in most tumors and the evdence of active secretion in some tumors.

DERMATOLOGIC EVALUATION OF YEAST, TYROTHRICIN, CHLOROPHYLL AND NITROFURAZONE

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THERE are many acceptable methods used in the treatment for pyoderma and infective allergic cutaneous diseases. The time-honored ammoniated mercury has produced good results, but it has a tendency to produce contact sensitization in a large number of patients. Methylrosaniline chloride and other chemical dyes are disagreeable to the patient. The sulfonamide drugs are frequently used by general practitioners in large amounts. Here again the severe and fatal reactions described during the last five years contraindicate their use except in unusual cases.

Even penicillin ointment has recently been condemned because of the present and future possibilities of sensitization. Also, certain strains of pyoderma-producing organisms that are resistant to sulfonamide drugs and penicillin are being observed. Nothing appears to be acceptable for any period of time. Dermatologists are confronted with the cases of toxicity and sensitization; consequently they are prejudiced and may be too critical.

The evaluation of any method of treatment must be compared with the treatment already accepted. The principles of surgery and internal medicine are the basis in healing and effecting a cure.

Stokes [1] has stressed for many years the importance of abnormal carbohydrate metabolism, congenital anomaly of fat secretion, gastrointestinal dysfunction, especially hypochlorhydria, elements of nervous stress, fatigue, overwork, strain and focal infection in the tonsils, teeth, sinuses, gallbladder or prostate gland. These are only a few factors that may excite or be the trigger mechanism in pyogenic cutaneous reactions.

ANTIBACTERIAL PROPERTIES OF YEAST (TORULOSPORA UTILIS VARIETY MAJOR)

The earliest mention found regarding antibacterial activity of yeast was by Sergent [2] in 1903, who reported a substance produced by yeast

1. Stokes, J. H.: The Eczema Problem, Am. J. M. Sc. **179**:69 (Jan.) 1930.

2. Sergent, E. P.: Levure de biere et suppuration, Ann. Inst. Pasteur **17**: 631, 1903.

which was toxic to Staphylococcus aureus. The observations and experimental evidence in the past sufficiently convinced Carpenter [3] to justify a more exhaustive study of the antibacterial property of yeast and yeastlike organisms. Yeasts are frequently mentioned in the lore of ancient materia medica. Only in the last few decades has their specific value in diets in deficiency diseases, furunculosis and abscess been correctly interpreted.

The yeast (Torulospora utilis variety major) was inoculated on sterile surgical gauze dressings. They were prepared individually in Petri dishes or in shingle arrangement in the bottom of suitable wide-mouth bottles or flasks. The yeast grows as a whitish gray mold across the gauze and permeates its fibers. They are ready in forty-eight to seventy-two hours, if incubated at about 30 C. All batches of yeast were checked by the Oxford cylinder.

The yeast-impregnated pads were kept moist with 5 per cent dextrose or sucrose solution. Such a dilution did not alter the potency, judged by the Oxford cylinder assay. The addition of sugar insures that the culture is a dynamic producer of inhibitory substances in situ. A part of the antibacterial effect of Torulospora utilis variety major may be attributed to the fact that it promptly increases the acidity of the medium or substrate to a p_H value below the tolerance of such pyogenic bacteria as Staph. aureus, Bacillus coli and Bacillus pyocyaneus.[3]

Study of Cases.—In 6 cases impetigo contagiosa was treated by cutting small squares of impregnated gauze which were applied to each lesion. These were changed daily and held in position with scotch tape and wax paper to prevent drying. All lesions were kept moist with sterile 5 per cent dextrose solution. In most cases the eruptions were due to hemolytic Staphylococcus albus and hemolytic Staph. aureus. All lesions were healed in five to ten days. No evidence of allergy was noted.

Ecthyma.—In 5 cases ecthyma of the lower extremities was treated with yeast-impregnated gauze. Three cultures yielded Staph. aureus and Staph. pyocyaneus. The lesions in 3 patients healed in seven days; in 2 they healed in twelve days.

Infectious Eczematoid Dermatitis.—In 5 cases of infectious eczematoid dermatitis the lesions were healed in ten to fifteen days. One patient failed to respond to treatment.

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3. Carpenter, C. W.: Antibacterial Properties of Yeasts, Fusarium Sp., Onion and Garlic, Hawaiian Planters Rec. **49**:41, 1945.

TYROTHRICIN

Dubos [4] in 1939 and Dubos and his colleagues [5] receive credit for isolating from bacteria specific chemical antibacterial substances. Tyrothricin is an extracted culture of a soil bacterium or an antibiotic substance obtained from Bacillus brevis, which is a mixture of gramicidin and tyrocidin.

The tyrothricin used in this study contained 1 mg. of tyrothricin per gram of vanishing cream base. Only the ointment was used in a clinical trial.

Impetigo Contagiosa.—Tyrothricin was used on 10 patients with impetigo contagiosa. Penicillin ointment, 500 units per gram, and 2.5 per cent ammoniated mercury ointment were used as controls. The patients were advised to debride all crusts, bullae and pustules before applying the medicament.

The lesions treated with tyrothricin healed in six to twelve days. The lesions treated with mercurial ointment were healed in six days. All lesions treated with penicillin healed in four to six days. The tyrothricin was soothing and well tolerated by all patients, but was not as effective as penicillin.

Sycosis Vulgaris.—In 5 patients with sycosis vulgaris there was temporary improvement but prompt relapse. These patients did not respond to penicillin ointment or ammoniated mercury ointment.

Ecthyma.—The lesions in 4 patients with ecthyma healed somewhat, then remained stationary. These lesions finallly healed with penicillin ointment. Cultures yielded hemolytic Staph. aureus and beta hemolytic streptococcus.

Infected Decubitus Ulcers.—These lesions in 3 patients improved during the first ten days and then failed to respond. The lesions later healed with parenterally administered penicillin and cod liver oil and urea ointment in three weeks.

Dermatitis Repens.—The lesions in 2 patients were satisfactorily healed in eight days. One of these patients had previously used penicillin, sulfathiazole and mercurial ointment, without benefit.

CHLOROPHYLL

Clinicians have been looking for an effective, nontoxic and noninjurious therapeutic agent which accelerates regeneration of cells in damaged tissues. There is great need for such an agent for the treatment of burns, wounds, ulcers and infective diseases of the skin.

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4. Dubos, R. J.: Bactericidal Effect of Extract of Soil Bacillus on Gram Positive Cocci, Proc. Soc. Exper. Biol. & Med. **40**:311 (Feb.) 1939.

5. Dubos, R. J., and Cattaneo, C.: Studies on a Bactericidal Agent Extracted from Soil Bacillus: Preparation and Activity of a Protein-Free Fraction, J. Exper. Med. **70**:249 (Sept.) 1939.

Centuries ago plants were used in an attempt to cure infected wounds and disease.[6] The Hawaiians and North American Indians have used the green portions of certain plants for the healing of infected wounds. Generations of families have passed on the family medicinal secrets of horseradish, onion, garlic and spinach. These medieval secrets have recently been exploited by the Russians.[7]

In 1913 Willstätter and Stall [8] discovered the empiric formula of chlorophyll. No serious effort was made before this time to evaluate the healing properties of essential green complex of plants—chlorophyll. Early studies of chlorophyll were concerned with its fundamental role in plant life. Its catalytic function in the complex process of converting carbon dioxide to starch by photosynthesis is well known.

Collings [9] stated that it has been shown conclusively that, of all the agents at present available for the stimulation of cell proliferation and tissue repair, chlorophyll probably has the most constant and decided effect. Chlorophyll acts on the tissues of the host rather than on the bacteria themselves.

"Chlorezium" [10] was used in the topical treatment of 55 patients with pyoderma, ulcers and allergic contact and atopic eczema. Twenty-five of these patients were treated with penicillin ointment (1,000 units per gram) as controls. All lesions were debrided and cleansed with detergent soaps before applying chlorophyll.

In patients with acute and subacute pyoderma chlorophyll ointment produced varied response. The lesions in 74 per cent of patients with impetigo contagiosa cleared in six to seven days. In 26 per cent the lesions were not cleared in ten days, and then another drug was used. The lesions in the control patients healed with penicillin were all cleared in seven days. In 3 patients with sycosis vulgaris there was no improvement and only temporary improvement with penicillin. In 12 patients with contact and atopic eczema, decided improvement was noted. The ointment was healing and soothing and failed to produce an irritating reaction. In 5 patients with chemical burns and sunburn the water-soluble cream was amazingly healing and soothing to the injured epithelium.

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6. Osborn, E. M.: On Occurrence of Antibacterial Substances in Green Plants, Brit. J. Exper. Path. **24**:227 (Dec.) 1943.

7. Tokin, B.: Phytoncides or Plant Bactericides: Effect of Phytoncides upon Protozoa, Am. Rev. Soviet Med. **1**:237-239 (Feb.) 1944; reviewed, Science News Letter, March 11, 1944.

8. Willstätter, R., and Stall, A.: Untersuchungen über Chlorophyll, Berlin, Julius Springer, 1913.

9. Collings, G. H., Jr.: Chlorophyll and Adrenal Cortical Extract in Local Treatment of Burns, Am. J. Surg. **70**:58 (Oct.) 1945.

10. Chlorezium ointment contains water-soluble chlorophyll derivatives in a hydrophilic base and is manufactured by Rystan Co., New York.

NITROFURAN COMPOUNDS

Nitrofurazone (5-nitro-2-furaldehyde semicarbazone) is one of the recently introduced successful therapeutic preparations used in the treatment of infective diseases of the skin. Downing and Hanson [11] gave promising reports regarding the use of the nitrofuran compounds. Previously there had been a paucity of information regarding their use, limitations and toxicity.

TABLE 1.—*Results of Treatment with a Chlorophyll Preparation and with Penicillin in Controls*

Name of Disease	Number of Cases	Average Duration	Culture	Results	Results with Penicillin (Control)
Impetigo contagiosa....	15	7 days	Staph. aureus	11 healed in 6 to 7 days; 4 slow in healing	All lesions clear in 7 days
Ecthyma.....	3	30 days	Staph. aureus; hemolytic streptococcus	2 healed in 10 days; 1 slowly improved	Lesions healed in 11 days
Infected, eczematoid dermatitis	6	12 days	Staph. aureus; hemolytic streptococcus	3 healed in 14 days; 3 healed with penicillin ointment	All clear in 8 days
Fungous (Trichophyton) disease, secondarily infected	7	5 days	Beta hemolytic streptococcus; Staph. aureus	5 healed in 7 days; 2 improved only	No control
Sycosis vulgaris.....	3	6 mo.	Staph. aureus; Staph. pyogenes	3 improved but relapsed	No improvement
Chronic indolent ulcers	4	9 mo.	Beta hemolytic streptococcus; Staph. aureus	All improved; 2 healed	1 improved; 1 flare-up with contact sensitization
Contact allergy.....	8	12 days	.....	5 healed; 3 improved	1 burned and irritated; no allergic reaction in 7 cases
Atopic eczema.....	4	4 yr.	.....	No reaction; soothing and bland	
Burns (coagulation and fulguration)	5	24 hr.	.....	No secondary infection; all healed in 12 to 15 days	

Nitrofurazone is a lemon-yellow crystalline compound, slightly soluble in water. It is almost insoluble in ether. Nitrofurazone is heat stable. Exposure to light produces some discoloration. It is chemically synthesized from the pentose sugars of oat hulls and bran.

Dodd and his associates [12] stated that nitrofurazone is bactericidal as well as bacteriostatic. Common pathogens of the skin, such as hemolytic

11. Downing, J. G.; Hanson, M. C., and Lamb, M.: Use of 5-Nitro-2-Furaldehyde Semi-Carbozone in Dermatology, J. A. M. A. **133**:299 (Feb. 1) 1947.

12. Dodd, M. C.; Hartmann, F. W., and Ward, W. C.: The Local Application of Nitrofuran Compounds with Special Reference to Use on Wounds, Surg., Gynec. & Obst. **83**:73 (July) 1946.

streptococcus and Staph. aureus, are rendered harmless even in the presence of blood and serum.

Nitrofurazone, or 5-nitro-2-furaldehyde semicarbazone, is impregnated with a water-soluble base, consisting of "carbowax" (75 per cent), a polyethylene glycol, and propylene glycol (25 per cent). The preparation becomes almost fluid at body temperature. The p_H lies between 5 and 7.

Nitrofurazone ("furacin" [13]) was used in the clinical evaluation of dermatoses in 75 patients. The disease in these patients was severe in epithelial destruction and varied from the acute to chronic pyoderma and allergic diseases of the skin. All control patients were treated with chlorophyll ointment and penicillin ointment for related healing and bactericidal effect.

Nitrofurazone maintained a high degree of effectiveness in all cases of pyoderma. The lesions of impetigo contagiosa healed in four to ten days. Penicillin had little advantage, except that speed of healing was increased with the deep crusted lesions. The lesions in patients with ecthyma were healed in ten days. The lesions in 2 patients with infectious eczematoid dermatitis failed to heal with nitrofurazone dressings and chlorophyll ointment. These promptly healed with penicillin cream. The lesions in the other 6 patients cleared satisfactorily. All patients with stasis and decubitus ulcers improved. Excellent epithelization occurred. Two of the patients needed pinch grafts to complete healing. Penicillin ointment produced a violent reaction in 2 of these patients.

Nitrofurazone was tested on extremely allergic sensitized skins. These sensitizations varied from acute contact dermatitis to atopic eczema. It was soothing and well tolerated by all patients. Epithelization was stimulated over the deep areas of excoriation. In 17 patients with burns, ranging from chemical ("lysol") to cautery and coagulation burns after removal of keratoses and epitheliomas, the skin healed faster with this preparation than with any other preparation used by me. The burned areas remained clean, free of secondary pyogenic crust.

COMMENT

Yeast preparations have been used clinically only to a limited extent. The type of inoculated gauze dressing is cumbersome for small superficial types of pyoderma. Large open lesions, such as decubitus ulcers, are ideal for treatment with this preparation. Yeast therapy has been useful in combating secondary infections with B. coli and B. pyocyaneus, but since the advent of streptomycin these bacteria can be easily eradicated.

13. "Furacin" is manufactured by Eaton Laboratories, Inc., Norwich, N. Y.

Yeast was used in this short series of cases only to determine its antibacterial effect in 16 cases of acute pyoderma. The clinical results were satisfactory in patients with impetigo contagiosa and ecthyma.

Tyrothricin consists of at least two substances—tyrocidin and gramicidin. It is a toxic antibiotic when given intravenously. No serious reactions were noted following its topical use. Franks and his associates [14] noted 4 cases of contact dermatitis following the use of the ointment. This, he expressed the belief, was caused by sodium mercuri-

TABLE 2.—*Results of Treatment with Nitrofurazone and with Penicillin and Chlorophyll Used in Controls*

Disease	Number of Cases	Average Duration	Culture	Results with Nitrofurazone	Results with Penicillin (Control)	Results with Chlorophyll (Control)
Impetigo contagiosa	13	8 days	Staph. aureus	10 healed in 4 to 10 days; 3 improved	All lesions in 10 cases healed in 7 days	All lesions improved in 5 cases; 3 healed in 8 days
Fungous (Trichophyton) disease, secondarily infected	5	12 days	Staph. aureus; beta hemolytic streptococcus	All improved in 3 days	3 improved (pyoderma)	All lesions improved in 3 cases
Ecthyma	4	21 days	Staph. aureus; Str. pyogenes; B. pyocyaneus	All improved; 3 clear in 10 days	2 improved, 1 failed to heal	1 improved
Infectious eczematoid dermatitis	8	20 days	Staph. aureus; beta hemolytic streptococcus	6 clear in 10 days	Healing in 2 cases only after using penicillin	
Stasis and decubitus ulcers	6	11 mo.	B. pyocyaneus; beta hemolytic streptococcus	All improved; 2 needed pinch grafts to complete healing	2 became worse (sensitization)	
Dermatitis repens	2	2 weeks	.....	2 improved	.....	Minimal improvement
Contact allergy	15	10 days	Mangal, gasoline, cement, etc.	Soothing healing effect in 14 cases; not tolerated in 1	.....	Soothing and healing in 10 cases
Atopic eczema	5	7 yr.	.....	4 tolerated medication; 1 complained of burning		
Burns (coagulation and fulguration)	17	24 hr.	.....	Excellent		

thiosalicylate in dilution of 1 to 40,000, used as a preservative in the ointment.

Tyrothricin was effective in patients with acute pyoderma, such as impetigo contagiosa, but little benefit was noted in those with sycosis vulgaris and secondarily infected eruptions.

Chlorophyll has the property of increasing cell metabolism and promoting physiologic repair of injured tissues.[15] Its toxicity has been

14. Franks, A. G.; Dobes, W. L., and Jones, J.: Tyrothricin in the Treatment of Diseases of the Skin, Arch. Dermat. & Syph. **53**:498 (May) 1946.

regarded as neglible when used topically, parenterally or by mouth.[16] Chlorophyll [15] acts on the tissues of the host rather than directly on the bacteria themselves. This feature is demonstrated by the topical application of chlorophyll in the rapid deodorization of malodorous chronic wounds infected by secondary anaerobic proteolytic bacteria. Patients with acute pyoderma responded satisfactorily. The best results were produced in superficial lesions. The preparation was ideal for the treatment of acute contact dermatitis. Atopic dermatitis was benefited when in the eczematoid and irritative stage.

The nitrofuran compounds have been observed to produce decided bacteriostatic activity in vitro.[17] Investigations [17] both in vivo and in vitro demonstrated the antibacterial action extended to many gram-negative as well as gram-positive organisms. The action was observed to be both bacteriostatic and bactericidal in the presence of body fluids.

The mechanism of the chemotherapeutic action of the nitrofuran compounds on the bacterial cell is not known. This antibacterial effect [12] is possibly produced by interference with the vital metabolic process of bacterial growth, resulting in destruction and death of the bacterial cells.

I was impressed with the healing of infected lesions of the skin treated with this preparation. The healing time of lesions treated with nitrofurazone closely paralleled the healing time of lesions treated with penicillin ointment used as a control. It appears to be a valuable addition for the treatment of burns. The lack of toxicity and low incidence of sensitization places this preparation in a unique field against the sulfonamide drugs, mercurial preparations, dyes and caustic chemicals.

The nitrofuran compounds cannot be placed above the proved penicillin preparations. Both preparations have their ideal situations in the treatment of infected diseases of the skin.

SUMMARY

Yeast (Torulospara utilis variety major)-impregnated gauze dressings were used for the treatment of 16 patients with acute to chronic pyoderma. The antibacterial properties of this yeast suggest unusual healing power. The mode of application and its troublesome manufacture render its clinical use undesirable.

Tyrothricin ointment was used for the treatment of 24 patients. This drug was effective for superficial impetiginous lesions, but had

15. Gruskin, B.: Chlorophyll—Its Therapeutic Place in Acute and Suppurative Disease: Preliminary Report of Clinical Use and Rationale, Am. J. Surg. **49**:49 (July) 1940.

16. Smith, L. W.: Chlorophyll: An Experimental Study of Its Water-Soluble Derivatives, Am. J. M. Sc. **207**:647 (May) 1944.

17. Dodd, M. D., and Stillman, W. B.: In Vitro Bacteriostatic Action of Some Simple Furan Derivatives, J. Pharmacol. & Exper. Therap. **82**:11 (Sept.) 1944.

no value for ecthyma and sycosis vulgaris. The drug is of little practical value in the treatment of ordinary diseases of the skin.

Chlorophyll ("chlorezium") offers a unique physiologic approach to the topical treatment of pyoderma, burns, ulcers and allergic sensitizations of the skin. It has good possibilities as a topical dressing, as it is a bland soothing nontoxic, cell-stimulating biotherapeutic agent.

The nitrofuran compounds (nitrofurazone ["furacin"] was used in the series described) are effective as antibacterial preparations for wound and surface infections. This new chemotherapeutic agent closely parallels the clinical results of penicillin ointment.

The late C. W. Carpenter prepared the yeast gauze dressings used in this study.

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DERMATITIS OF THE HANDS

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DERMATITIS of the fingers and hands is often a baffling disease with a record of a disconcertingly high percentage of failure in treatment.[1] Inasmuch as this etiologically heterogeneous disease constitutes approximately 10 per cent of all cases seen in dermatologic practice,[2] methods of treatment which will yield cures consistently are of the greatest utility to physicians and to patients. The presence in both private and clinical practice of a considerable number of patients with dermatitis of the hands, frequently of many years' duration and resistant to previous treatment, stimulated the formulation of views herein presented.

Most of the patients in this study had previously sought professional relief, to no avail.[3] Some had received irradiation therapy to tolerance. All had received various medicaments to apply to the skin, the composition of which suggested that antipruritic palliation seemed to be prized, and the likelihood of producing additional irritation seemed often overlooked. Several patients had submitted to a great number of allergy tests, hyposensitizing injections and various elimination diets, without cure. There are two pitfalls in relying on the results of allergy tests, either patch or intracutaneous:

1. One cannot be certain that the substance primarily responsible is included among the test substances used.

2. Many substances yielding negative reactions on uninvolved skin may irritate the affected skin.

A plan for circumventing these pitfalls and directed toward the causative factors consists in elimination of all contact irritants, treatment for local infection, when present, with drugs rarely productive of irritation and eradication of focal infection in cases of long standing. Should the institution of these measures prove ineffective, ingestant or inhalant allergens should be suspected. Elimination diets for food

1. Tobias, N.: Eruptions on the Hands: Their Diagnosis and Treatment, South. M. J. **39**:336-344 (April) 1946.

2. Lane, C. G.; Rockwood, E. M.; Sawyer, C. S., and Blank, I. H.: Dermatoses of the Hands, J. A. M. A. **128**:987-993 (Aug. 4) 1945.

3. The cases reported were studied in association with Dr. Richard L. Sutton Jr., who gave helpful criticism.

allergens and hyposensitization for inhalant allergens are not recommended prior to these procedures.[4]

It has been estimated that 36 per cent of patients with dermatitis of the hands are not etiologically classifiable.[5] I believe that the method of elimination and subsequent identification of contact irritants described herein, together with the eradication of focal infection, will appreciably diminish this high and previously baffling percentage. So-called recurrent resistant vesicular eruptions of the hands,[6] pompholyx and vesiculopustular lesions respond to these measures.

DIAGNOSIS

As in all disease, adequate diagnosis is prerequisite to treatment. The following outline is of the causes of diseases of the hands:

A. Physical Agents
   1. Friction
   2. Humidity
B. Contact Irritants
   1. Medicinal chemicals
   2. Cosmetics
   3. Household chemicals, such as cleansing agents
   4. Occupational chemicals
   5. Contact irritants in pursuit of hobbies
   6. Foods
   7. Apparel
   8. Plants and animals
C. Contact irritant plus secondary infection
D. Contact irritant plus focal infection
E. Infectious agents (which may be mixed)
   1. Herpes and other viruses
   2. Staphylococci, streptococci and other bacteria
   3. Fungi
   4. Scabies, mites and other metazoa
F. Ingested, injected or inhalant chemicals
   1. Medicines
   2. Foods
   3. Inhalants
      (a) pollens
      (b) nonpollens (house dust, horse dander, silk and the like)
G. Focal infection of teeth, gums, tonsils, sinuses, prostate, anus and rectum, pelvic and genitourinary organs, nails and bronchi
   1. Gonorrheal dermatoses, exanthems and keratoses
   2. Pustular bacterid
   3. Dermatophytid
   4. Chronic dermatitis
H. Diseases of unknown causation
   1. Psoriasis
   2. Seborrheic dermatitis
   3. Herpetoid (nummular) dermatitis
   4. Lichen planus
   5. Erythema multiforme
I. Avitaminoses and metabolic disturbances
   1. Pellagra
   2. Pityriasis rubra pilaris
   3. Xanthoma
J. Other diseases of the hands to be distinguished from dermatitis (including malformations and neoplasms)
   1. Epidermoylsis bullosa
   2. Keratosis follicularis
   3. Keratosis palmaris et plantaris
   4. Arsenical keratoses
   5. Irradiation epithelioma
   6. Hemangiosarcoma of Kaposi

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4. Rowe, A. H.: (*a*) Atopic Dermatitis of the Hands Due to Food Allergy, Arch. Dermat. & Syph. **54**:683-703 (Dec.) 1946; (*b*) Dermatitis of the Hands Due to Atopic Allergy to Pollen, ibid. **53**:437-453 (May) 1946.

5. Andrews, G. C., and Barnes, M. C.: Pustular Bacterids and Allied Conditions, South. M. J. **34**:1260-1266 (Dec.) 1941.

6. Blaisdell, J. H., and Swartz, J. H.: Recurrent Resistant Vesicular Eruption of Hands, Arch. Dermat. & Syph. **51**:365-369 (June) 1945.

Such an outline suggests that proper diagnosis requires answers to three basic questions:

1. Is the disease due to external or internal agents?
2. Is the disease due to physical or chemical agents or to parasites?
3. To what extent is the disease due to a multiplicity of such factors?

In dermatitis of the hands the factors most frequently operative are external and chemical.[7] Although staphylococci are commonly seen in cultures taken from these lesions,[2] they are likely to appear as secondary invaders in skin first injured by chemicals. This is understandable when consideration is given to the fact that in all kinds of employment use of the hands is essential, whether the worker be an unskilled laborer or a trained surgeon. Each job provides a specific environment for hands, and this environment is composed of chemicals. Over 50 per cent of all occupational dermatoses affect the hands.[1] The occupational environment of housewives is at least equally complex chemically.

Inasmuch as hands exist in a physical and chemical environment which may result in trauma to the skin, dermatitis due to internal or infectious agents is benefited by protection from contact irritants. Failure to recognize this fact or, if recognized, failure to instruct patients adequately in the manner of avoiding these irritants is, I believe, a frequent cause of failure of treatment in the infectious cases. It is because of the removal from contact irritants in the patients' home or business that patients with intractable disease often recover quickly when hospitalized, although the treatment has not otherwise been changed.

It is to be noted that no distinction is made here among primary irritation, hypersensitivity and externally caused allergic disease. This is because these three groups of contact irritants must all be eliminated to effect cure.

DERMATITIS VENENATA

Identification of the chemical agent producing the dermatitis may occasionally be disclosed by history alone, or history may suggest that one of a small number of chemicals is suspect. More often it is not possible to exclude the likelihood that one or more of a great number of environmental contact irritants is responsible. In these instances, all contact irritants must first be eliminated and a method of subsequent identification of those etiologically related must then be provided.

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7. Stokes, J. H.; Lee, W. E., and Johnson, H. M.: Contact, Contact-Infective and Infective-Allergic Dermatitis of the Hands, with Special Reference to Rubber Glove Dermatitis, J. A. M. A. **123**:195-202 (Sept. 25) 1943.

METHOD OF ELIMINATION OF CONTACT IRRITANTS AND THEIR SUBSEQUENT PRECISE IDENTIFICATION

Accepting the importance of elimination of environmental irritants in the management of dermatitis of the fingers and hands, the method of achieving this requires consideration. The patient is questioned regarding occupation, habits, hobbies, time of appearance of the disease, seasonal incidence and other possibly related factors. An attempt is made to educate the patient in regard to the role of external chemicals. Illustrative cases may be cited to him. His understanding, cooperation and intellectual conviction of the correctness of and necessity for this approach are sought. He is informed that his dermatitis is not due to "nerves," not due to "something wrong with the blood," not due ordinarily to what he eats [8] and not due to worry. He is instructed that cure does not depend on medicine put on the skin but that cure will result from keeping chemicals off the skin. Previous external and internal medication is stopped. The following list of forbidden and permitted substances is then reviewed with the patient.

Forbidden	Permitted Substitution
Friction	Relief of itching by use of towel moistened with cold water
Scratching	Not permitted
Excessive heat	Not permitted
Excessive cold	Not permitted
Excessive moisture	Dry hands with cotton cloth; powder liberally with corn starch
Hair oil	Water or petrolatum to make hair more tractable in combing
Hair tonic	Not permitted
Washing own hair	Hair washed by other member of family, beauty parlor or barber shop, using a specified rarely irritating detergent ("Lux" toilet soap is seldom observed to cause trouble.)
Powder	Corn starch or zinc oxide tinted with powdered calamine, if desired
Mascara	Not permitted
Perfume and cologne	Not permitted
Cold cream	Not permitted
Lipstick	Hypoallergenic type which may be applied also to cheeks as rouge (Marcelle and Almay manufacture hypoallergenic products.)
Rouge	Not permitted
Brushless shaving cream	Brush and specified rarely irritant soap lather (in our experience "palmolive" shave cream rarely irritates) or electric shaver
After-shave lotion	Water
Soap	Cleanse with water only
Soap substitute	Member of family may bathe patient with specified rarely irritating detergent ("Lux" toilet soap seldom causes trouble.)
Cleansing agent or detergent of any type	Water and petrolatum only
Tooth powder, paste or cleanser for prostheses	Baking soda and water
Eye drops or eye medication	Isotonic solution of sodium chloride only
Mouthwash	Water or isotonic solution of sodium chloride
Nail polish	Not permitted
Nail polish remover	Acetone, once, without smearing
Hand lotion or cream	Plain white petrolatum spread thinly and excess wiped off with cotton cloth
Deodorant liquid or cream	Sodium bicarbonate (Lamb, J. H.: Sodium Bicarbonate, an Excellent Deodorant, *J. Invest. Dermat.* **7**: 131-135 [June] 1946.)
Emery board	Scissors or nippers
Washing dishes	Water only
Washing clothes	Hire the job done

8. Dermatitis of the hands due to food only is uncommon.

Forbidden	Permitted Substitution
Cleansers for bath, floor, sink, windows	Water only
Cleaning fluids	Water only
Furniture polish	Clean dry cloth
Water softeners	Not permitted
Steel wool for pans	Not permitted
Household insect powders or sprays	Not permitted
Moth preventives	Not permitted
Garden insecticides and sprays	Not permitted
Plants and flowers	Not permitted
Paint	Not permitted
Turpentine	Not permitted
Ammonia water	Not permitted
Silver polish	Not permitted
Glue	Not permitted
Disinfectants	Not permitted
Sulfonamide drugs	Not permitted
Medicine cabinet supplies	Not permitted
Ink remover	Not permitted
Antiseptic baby oil	Liquid petrolatum
Athlete foot powder or ointment	Corn starch powder
Shoe polish	Not permitted
Matches	Lighter
Jewelry and rings	Not permitted
Handling flavoring extracts, cinnamon, peppermint, etc.	Not permitted
Flour	Purchase bakery products
Handbag: plastic, leather or rayon (customary contents of handbag are checked)	Cotton or linen handbag, containing only permitted articles
Plastic, lacquered, rubber or leather articles acquired shortly before or after the onset of the disease	Old materials
Steering wheel	Not permitted
Wool clothes	Cotton or linen clothing
Wool blankets	Cotton blankets
Husband's or wife's use of toiletries	Not permitted in rare cases
Additional substances elicited by inquiry regarding occupation and hobbies. Such information is often extremely fruitful	Off the job

Occasionally the patient's initial response is, "How can I live in this manner?" More often, however, the patient has previously attempted food elimination diets and has received numerous injections and similar, but not sufficiently inclusive, instructions, so that he is broken to the harness. Miserable with persistent disease of the hands, he is not only willing but anxious to do what he is asked. The patient is informed that it will be necessary to live in an extremely restricted manner for probably only ten days. If the dermatitis improves as expected during this time, he is ready to start testing the forbidden substances.[9]

The items restored first are those the deprivation of which causes the patient the most inconvenience. Each day one previously forbidden article is tested by using it in the ordinary way. The appearance of a flare is evidence that the last product restored is not tolerated and must be retested before it can be used by the patient in the future. As soon as the flare subsides, the process of adding items is continued. Particular brands of products, such as soap, cosmetics or toiletries, are specified. If the patient does not tolerate the use of any brand of an essential product, such as soap, he must avoid it. The articles handled by the patient while at work must be restored individually in a similar manner.

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9. Sutton, R. L., Jr.: Contact Dermatitis: Simplification of Therapy and of the Search For Causes, J. Missouri M. A. **44**:481-484 (July) 1947.

LOCAL TREATMENT

The physician must refrain from the use of drugs that may produce additional irritation. One may successfully rely on the physical characteristics of medicaments for relief of symptoms rather than their chemical properties. Distressing pruritus is relieved by application of a nonmedicated cool moist water compress. The physical properties of coolness and moisture are as effective in allaying itching or burning as any chemical antipruritic. Fissuring due to excessive dryness is relieved and prevented by the physical properties of an inert paste, such as zinc oxide powder in petrolatum. A paste is sufficiently lubricating to prevent excessive dryness and yet is not so greasy, if sparingly applied, as to interfere with the physiology of healing. As soon as possible all local medication is discontinued.

Irradiation therapy is never given during the first visit, being withheld until several days have passed and it has become apparent that the patient comprehends and follows his instructions. To do otherwise would be to dissipate a strictly limited therapeutic agent, for irradiation will not cure contact dermatitis but will only allay it. It is best given after the cause, though specifically undetermined, has been eliminated.

Patients with autonomic imbalance resulting in volar hyperhidrosis are instructed to dry their hands frequently with a cotton cloth and to apply corn starch powder liberally.

REPORT OF CASES OF CONTACT DERMATITIS

CASE 1.—R. N., a housewife aged 37, was seen April 2, 1946, with red scaly dermatitis of the dorsum of the hands and the sides of the fingers of six months' duration. She was instructed in the avoidance of contact irritants. By April 16 the disease had cleared, and the testing of one new item each day was started. The day she held flour in order to bake, the hands and fingers flared. The handling of flour was not permitted thereafter, and she has remained free of disease to date (Jan. 6, 1947).

Comment.—The agent specifically responsible for recurrence of the disease was identified with precision among the multiplicity of objects handled by the method of testing one new item daily.

CASE 2.—S. P., a housewife aged 32, was seen Feb. 22, 1946, with erythematous scaly dermatitis of the dorsum of the hands and fingers of twelve months' duration. She was instructed in the avoidance of contact irritants and was free of disease on March 13. Soaps and cleaners would produce recurrence. It was recommended that she use a mild toilet soap once a day only for the hands and that she wear impervious gloves, rarely observed to be irritating,[10] for washing (dishes, the children's bath). She has remained free of disease to date (Jan. 6, 1947).

Comment.—Intolerance of soap or other detergents is frequent. Application of detergents to one's face, body, children or articles of clothing multiplies the incidence of contact of detergents with the hands.

10. "Stanzoil" ("neoprene") gloves seldom irritate.

CHRONIC DERMATITIS

Removal of foci of infection is frequently as important in dermatitis of the hands of long standing, usually of more than four months' duration, as it is in pustular bacterids.[5] Cure is obtained in these patients when contact irritants have been eliminated and sources of infections have been methodically sought out and eradicated. Teeth and gums, tonsils, prostate, pelvic disease, feet and nails are considered first. Sinuses, bronchi and urinary tract are next in line. Roentgenograms of the teeth are routinely requested of these patients, and teeth with root abscesses or root canal work are extracted. Pyorrhea must be treated. Examination of prostatic secretion is made, without regard to history of gonorrhea. These patients may be given penicillin in oil daily while foci are being cleared.[11] The rapidity of healing with this treatment of dermatitis of long duration is often gratifying.

CASE 3.—C. C., a farmer aged 70, was seen June 26, 1946, with vesicular and scaling dermatitis of the dorsum of the hands of fifty years' duration. Soap "set his hands on fire." He was instructed in the avoidance of contact irritants. Prostatic fluid showed no increase of pus cells, but dental films showed abscessed teeth and pyorrhea. The necessary extractions were made on July 6 and July 13, and the patient received 300,000 units of penicillin in oil daily during the period of extractions. On July 30 his hands were free of disease, and they have remained free to date (Jan. 6, 1947).

INFECTIOUS ECZEMATOID DERMATITIS

Effective treatment of vesicular staphylococcic dermatitis of the hands, infectious eczematoid dermatitis,[12] requires elimination of contact irritants together with chemotherapy against the infectious organisms. Foci of infection are sought out and removed, as in dermatitis of long duration. Penicillin in oil, 300,000 units daily, is given intramuscularly for four days. Local applications vary with the stage of the dermatitis. Weeping crusted lesions call for the use of moist compresses, and aluminum acetate, ¼ level teaspoon of the powder to 1 quart of cool water, is rarely injurious. Compresses are applied four to six times a day for periods of twenty to sixty minutes. They should not be permitted to become dry during their application, but should be remoistened frequently, rinsed occasionally in running water and boiled once a day. A thin layer of a thick paste, such as 1 part zinc oxide powder in 3 parts solid petrolatum, is applied at bedtime to prevent excessive drying and fissuring overnight. Resistant vesicular and pustular lesions may be treated with solution of potassium permanganate, made

11. Dennie, C. C., and Morgan, D. B.: Use of Large Daily Injections of Penicillin Emulsion in Dermatology, J. Missouri M. A. **43**:539-541 (Aug.) 1946.

12. Engman, M. F.: An Infectious Form of an Eczematoid Dermatitis, Am. Med. **4**:769-773 (Nov. 15) 1902. Lane, Rockwood, Sawyer and Blank.[2]

by adding 1 drachm of a 6 per cent solution to 1 quart of warm water, for fifteen minutes three times a day. A red but fairly dry surface may be painted once daily with 2 per cent aqueous solution of methylrosaniline chloride. Fissures may be painted with 5 per cent aqueous solution of silver nitrate once daily.

CASE 4.—J. S., a housewife aged 20, was seen May 24, 1946, with patchy vesicular dermatitis of the hands and fingers present for six years. A focus of infection could not be found. She was instructed in the avoidance of contact irritants. Penicillin in oil, 300,000 units daily, was given for four days. Compresses moistened with solution of aluminum acetate were applied four times a day for twenty minutes. On June 22 the fingers and hands were clear of disease, and they have remained clear to date (Jan. 6, 1947).

RECALCITRANT VESICULOPUSTULAR ERUPTIONS

The necessity for eradicating focal infection in the treatment of recalcitrant vesiculopustular eruptions has been repeatedly emphasized.[13] My observations confirm these studies, and the elimination of contact irritants has been observed to be of additional value. When skin is already damaged by toxins, the application of detergents, antipruritics and other chemicals frequently serves only to augment and prolong disease.

CASE 5.—J. W., a student aged 21, was seen Aug. 28, 1946, with the palms and fingers nearly completely covered by vesicopustules. A vesiculopustular eruption first developed on the palms in March, which cleared slowly with hospitalization and varied treatment, including irradiation and penicillin. In May the eruption recurred and again healing was slow. On August 17 the disease recurred. A search had not previously been made for focal infection. Roentgenograms of the teeth showed abscesses of the upper left central and lateral incisors. They were extracted, and penicillin in oil, 300,000 units daily, was given for three days. The patient was instructed in the avoidance of contact irritants, and the only local treatment permited was with solution of potassium permanganate in dilution of 1 to 5,000. The patient was free of disease on September 7, ten days after he was first seen, and has remained free to date (Jan. 6, 1947).

DERMATOPHYTIDS

Vesicular eruptions of the hands associated with dermatophytosis elsewhere are commonly recognized today.[14] The high incidence and characteristic distribution of vesicular eruptions resulting from injec-

13. Andrews, G. C.; Birkman, F. W., and Kelly, R. J.: Recalcitrant Pustular Eruptions of Palms and Soles, Arch. Dermat. & Syph. **29**:548-563 (April) 1934. Wise, F., and Wolf, J.: Problems in Diagnosis and Treatment of Recurring Vesicular Eruptions of the Hands, New York State J. Med. **40**:1573-1578 (Nov. 1) 1940. Carpenter, C. C.: Management of Recurrent Vesiculo-Pustular Eruptions of Hands and Feet, J. M. Soc. New Jersey **42**:262-267 (Aug.) 1945.

14. Peck, S. M.: Epidermophytosis of the Feet and Epidermophytids of the Hands, Arch. Dermat. & Syph. **22**:40-76 (July) 1930.

tions of penicillin, as high as 25 per cent in patients with cutaneous disease,[15] and often limited to or starting in the feet, hands and crural regions, suggest that similar vesicular eruptions associated with distant mycotic infection are due to analogous absorption. Treatment of dermatophytids frequently requires the avoidance of contact irritants as well as eradication of the primary focus.

CASE 6.—C. H., an office worker aged 43, was seen June 14, 1946, with vesicular scaling dermatitis of the fingers and hands present for two years. Examination revealed chronic dermatophytosis of the feet. He was instructed in the avoidance of contact irritants; mild fungicides were applied to the feet, and corn starch powder was used liberally between the toes and in the hose and shoes to absorb moisture and to provide a dry environment. On July 3 both hands and feet were clear, and they have remained clear to date (Jan. 7, 1947).

MONILIAL INFECTION

In dermatitis of the hands due to specific infectious agents, such as Monilia organisms, the elimination of contact irritants frequently is as necessary as the specific medication applied.

CASE 7.—J. C., a housewife aged 47, was seen April 6, 1946, with interdigital moniliasis (erosio interdigitalis blastomycetica) of twenty years' duration, which had been treated from time to time with various acceptable topical applications. She had never received adequate instruction in the avoidance of soap, cleansing agents and prolonged immersion in water. Two per cent aqueous solution of methylrosaniline chloride was applied in the acute stage of the disease and 3 per cent chrysarobin in chloroform in the subacute stage. Involvement of the finger nails, present during at least the past year, also was treated. By April 26, three weeks later, the formerly intractable interdigital infection was cured.

ATOPIC DERMATITIS

Inhalant and ingested allergens have been cited as causes of dermatitis of the hands.[16] The role of atopens in the production of dermatitis elsewhere on the body has been repeatedly demonstrated,[17] although interpretation of the term "atopic" has been controversial.[18] If patients for whom this diagnosis is contemplated are given proper detailed instructions in the avoidance of contact irritants, if local

15. Kolodny, M. H., and Denkoff, E.: Reactions in Penicillin Therapy, J. A. M. A. **130**:1058-1061 (April 20) 1946.

16. Rowe,[4] White, C. J.: Allergy in Diseases of the Skin, M. Clin. North America **18**:1253-1262 (March) 1935.

17. Sulzberger, M. B., and Vaughan, W. T.: Experiments in Silk Hypersensitivity and the Inhalation of Allergen in Atopic Dermatitis (Neurodermotitis Disseminatus), J. Allergy **5**:554-560 (Sept.) 1934. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940.

18. Cooke, R. A.: Consideration of Some Allergy Problems: Allergic Dermatitis (Eczema), J. Allergy **15**:203-211 (May) 1944. Urbach, E.: The Concept of Atopy in the Light of Recent Investigations, Arch. Pediat. **58**:482-494 (Aug.) 1941.

infection when present is treated with drugs rarely productive of irritation and if focal infection is sought out and eradicated, few patients remain for whom the diagnosis would be dermatitis due to ingestants or inhalants. These remaining patients may hopefully be given elimination diets.[19] The role of contact irritants in these persons still should not be overlooked, for dermatitis of the hands due to ingested or inhalant allergen may not respond to food elimination or inhalant hyposensitization procedures until strict avoidance of contact irritants is also obtained,[4a] and the fact is illustrated by Rowe's [4b] patient (case 3), whose dermatitis of the hands allegedly due to hypersensitivity to pollen would flare after washing dishes or clothes or after the use of turpentine to remove paint from her hands. Furthermore, treatment by hyposensitization of dermatitis of the hands allegedly due to pollens has required as much as two years to succeed,[4b] a period long enough for cure to be as satisfactorily accounted for by other hypotheses, such as change in chemical environment or "hardening." [20] Dermatitis of the hands in persons with atopic dermatitis may be due to a contact irritant or infection, which is not relievable by elimination diet.

CASE 8.—M. G., a stenographer aged 23, was seen Oct. 2, 1946, with vesicular and erythematous scaling dermatitis of the dorsum of the hands and fingers present for two years. Erythematous papular dermatitis of the cubital fossae had been present for eleven years. Allergic rhinitis due to pollen (her father also had allergic rhinitis) had been present for two years and under hyposensitization treatment (ragweed, cocklebur) by an allergist, with control of symptoms since March. Dermatitis of the fingers and hands did not improve with pollen hyposensitization, so that she was given elimination diets by the allergist. These were without benefit, so that she resumed an unrestricted diet and was referred for dermatologic management. She was instructed in the avoidance of contact irritants and received "pyribenzamine hydrochloride" N.N.R. (tripelennamine hydrochloride), 100 mg. after each meal and 150 mg. at bedtime from October 2 through October 9, with only slight improvement. "Pyribenzamine hydrochloride" was discontinued, and she received 300,000 units of penicillin in oil daily from October 11 to October 15, by which time her fingers and hands became free of disease and have remained free to date (Jan. 16, 1947), although the cubital dermatitis has remained variable.

SUMMARY AND CONCLUSIONS

Dermatitis of the hands is frequently of complex causation. Although most cases are due initially to contact with irritant chemicals, many become complicated by infection, exogenous, or from foci or both.

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19. Rowe, A. H.: Elimination Diets and the Patient's Allergies: A Handbook of Allergy, Philadelphia, Lea & Febiger, 1941. Flood, J. M., and Perry, D. J.: Recurrent Vesicular Eruptions of the Hands Due to Food Allergy, J. Invest. Dermat. **7**:309-327 (Dec.) 1946.

20. Schwartz, L.: Occupational Dermatoses: Treatment and Prevention, J. Michigan M. Soc. **39**:179-180 (March) 1940.

Improvements in methods of treatment are described, and these increase the proportion of cures obtainable:

(*a*) Elimination of irritants is carried out in infectious and presumptively atopic as well as contact dermatitis.

(*b*) Procedure is detailed to accomplish the elimination and subsequent identification of the contact irritants responsible in each case,

(*c*) Foci of infection are eradicated in chronic dermatitis,

(*d*) Topical medication is limited to agents judged both effective and dependably nonirritant.

Elimination diets for food allergens and hyposensitization for inhalant allergens are measures of last resort for the small percentage of cases in which the previously described efforts prove not curative.

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SEROLOGIC CONFLICT

A Study of Serodiagnostic Discrepancies

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THE HISTORY of serology is punctuated throughout with the uncertainties presented to the minds of both serologists and clinicians by serologic conflict. This may be defined as differing reports on reactions in two or more types of blood tests for syphilis, whether from the same laboratory or from different sources. Inevitably the reporting of one reaction as positive and the other as negative on the same blood specimen must prove confusing to a physician. It is right and natural, then, that physicians and serologists should seek to eliminate conflict as far as possible and should endeavor to understand the probable causes behind the irreducible minimum of serologic discrepancy.

I have had experience with serologic tests for syphilis in large public health laboratories doing a heavy volume of work and also in a hospital laboratory handling a smaller number of specimens. The public health laboratory is apt to receive a larger percentage of normal blood specimens than is the hospital. Examination of results obtained from 6,792 tests made with the Kolmer modification of the Wassermann procedure and the Kahn standard procedure in a public health laboratory showed 268 cases of serologic conflict, or a little less than 4 per cent. This includes not only those cases in which there was positive reaction in one test as against a negative reaction in the other, but also those which involved a negative-doubtful report. One hundred and seventy-three of these reactions were positive or doubtful with the Kahn procedure and negative with the Kolmer, while 95 were positive or doubtful with the Kolmer technic as opposed to the negative Kahn reaction. The specimens for which the reaction proved positive with one test and doubtful with the other are not included in this study, inasmuch as they represent, in the vast majority of cases, a difference in degree rather than in kind. Of the 95 cases in which the Kolmer test elicited a positive reaction as against a negative diagnostic Kahn, 27 of these results were upheld by the results for the more sensitive presumptive Kahn test, which is run coincidentally with the standard test but is not reported. Disagreement of less than 4 per cent may be con-

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sidered a healthy margin. Comparative studies in other laboratories show results ranging from 69 per cent to 96.7 per cent agreement.

In the hospital laboratory, 1,970 tests with Kolmer Wassermann and Kahn standard methods yielded 7 discrepancies, which is 0.4 per cent of the total. That this is a distinct improvement over the record of the public health laboratory may be admitted and accounted for at least in part by the fact that the hospital obtains freshly drawn specimens and has a higher percentage of suspected and known cases of syphilis in the total series of positive reactions.

Holding serologic conflict to the minimum involves unceasing vigilance on the part of serologists. The avoidance of technical error, scrupulous care in the cleansing of glassware, conscientious preparation and titration of reagents and strict adherence to the standard methods as outlined by the authors of the tests performed—all these play a highly significant part in the avoidance of unnecessary discrepancies. Physicians have their contribution to make early in the procedure. If a sufficient amount of blood (at least 5 cc.) is sent in, properly taken in a clean and dry syringe, to avoid contamination and hemolysis, and sent to the laboratory promptly (since aging affects serologic potency), the finest technical effort obtainable is warranted.

In spite of the best precautions which can be taken by physicians and by laboratorians, in every laboratory in which more than one type of diagnostic test for syphilis is performed a certain percentage of conflicting reactions will be observed. The reasons for this may be divided into three categories: first, those inherent in the technical procedures, second, those which are factors of the serum, in relation to reagin content or independent of it, and third, those which involve the condition of the person whose blood is being tested.

The first group of causes of serologic discrepancy includes differences in sensitivity of the antigens used in the tests under scrutiny. As would be expected, in the majority of cases that test which employs the more sensitive antigen will give the larger number of positive reactions. Not completely understandable are those instances in which the ordinarily less sensitive antigen picks up a positive reaction which the more sensitive reagent has passed by. That zone phenomena are responsible for many of these reactions is probable, according to a number of investigators, including Hodel.[1] An excess of reagin can account for a false negative reaction in a flocculation test. A quantitative procedure is of value in these cases.

The sensitivity of an antigen depends on various conditions, such as freedom from impurities, the lipid concentration, the method of dilution with saline and the cholesterol content. In itself the cholesterol

1. Hodel, G. H.: The Clinician and the Serologic Report: Key Problems in the Serodiagnosis of Syphilis, Ven. Dis. Inform. **23**:215-221, 1942.

(or other sterol) plays no part in the reaction, but serves as a particulate core on which the adsorption process of antigen-reagin combination can build. Reagin is the reactive substance of the serum globulin.

Differences in the technic employed account for some discrepancies. While both the complement fixation and the flocculation procedures depend on that component of the serum globulin called reagin, which unites with antigen in the one case to fix complement and in the other to form visible aggregates, each test constitutes a different approach. The variability of complement, its liability to rapid deterioration and the fluctuations in sheep cell fragility all demand extreme care in control and compensation and are directly proportional to tendency to error. Mohr and Smith [2] ascribed what was long considered the results of daily variation in reagin content of syphilitic serum entirely to differences in the hemolytic system. The use of spectrophotometric methods, as described by Mayer, Eaton and Heidelberger,[3] for the standardization of complement may lead to greater accuracy in control methods for complement fixation tests. As to flocculation methods, any tendency toward the formation of nonspecific aggregates, either mechanical or biologic, and the undeniable personal element in the reading of results may complicate the use of the reaction.

Serologic discrepancy due to serum factors apart from reagin content may be attributed to the presence in the serum of native amboceptor for sheep red blood cells. This excess of amboceptor tends to decrease the sensitivity in a complement fixation test for that particular serum, while it can in no way affect a flocculation reaction. A situation such as this may frequently give rise to a report of a negative Wassermann as against a positive Kahn reaction. Noguchi [4] and Kolmer [5] both evolved methods of removing native amboceptor from serum, which increase the accuracy of the test, but the advantages do not compensate in every case for the technical difficulties involved when a large number of tests are to be performed.

Another difficulty leading to deviating reports lies in what Eagle [6] spoke of as the inhibiting action of serum on complement fixation. This

2. Mohr, C. F., and Smith, C. A.: On the Supposed Daily Variation of Reagin Content of Syphilitic Serum, Am. J. Syph., Gonor. & Ven. Dis. **24**:322-329, 1940.

3. Mayer, M.; Eaton, B., and Heidelberger, M.: Spectrophotometric Standardization of Complement for Fixation Tests, J. Immunol. **53**:31-35, 1946.

4. Noguchi, H.: The Laboratory Diagnosis of Syphilis: A Manual for Students and Physicians, New York, Paul B. Hoeber, 1923.

5. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technique, New York, D. Appleton-Century Company, Inc., 1945.

6. Eagle, H.: The Laboratory Diagnosis of Syphilis; The Theory, Technic, and Clinical Interpretation of the Wassermann and Flocculation Tests with Serum and Spinal Fluid, St. Louis, C. V. Mosby Company, 1937.

is a cause of zone reactions in a quantitative Wassermann test, in which the whole serum may appear to give a negative result while dilution of the same serum will prove positive. Boerner and Lukens [7] and Kolmer [8] introduced the use of egg albumen to obviate prezone reactions. This inhibitory action of serum does not significantly affect the flocculation reaction. Fortunately, in a Wassermann test such as the Kolmer, which involves refrigerator fixation, the inhibitory factor, associated with the serum protein, is kept at a low level by the temperature at which the fixation takes place.

Zone reactions occur in the flocculation tests, due apparently to excess of reagin content of the serum tested. Kahn [9] reported an "optimal zone reaction" test which takes into account the difficulties of the quantitative relationship between high reagin content of a specific serum and the antigen used. With this test a number of otherwise negative flocculation reactions are observed to be positive.

Finally, discrepancies in serum diagnosis occur because of the condition of the patient at the time the blood is taken. A large laboratory which receives daily specimens into the thousands must necessarily test blood specimens from all stages and degrees of syphilitic involvement, as well as those from persons, sick or well, in a state productive of a nonspecific positive reaction during the course of serologic tests. In the case of secondary syphilis, the percentage of positive reactions should run close to 100 for each type of blood test. In primary syphilis the amount of reagin in the blood may have reached the threshold of detection by a slightly more sensitive test, only to fail of discovery by a less sensitive procedure. In tertiary and congenital syphilis and in neurosyphilis, as well in untreated patients as in those receiving treatment, there are bound to be variations in serologic reactions for different procedures, because of proportional variation of syphilitic antibody in the circulation.

Add to the problems related to specimens from admittedly syphilitic patients those difficult and as yet imperfectly understood problems of the biologic type antibody which produces a false positive reaction in either a Wassermann, a Kahn or both tests, and the picture is complete. Beerman [10] reviewed this subject. The literature is full of experiment and speculation on febrile diseases of widely divergent types which pre-

7. Boerner, F., and Lukens, M.: Use of Egg Albumin as Protective Protein in Spinal Fluid Wassermann Test, Am. J. Clin. Path., Tech. Supp. **5**:71-74, 1941.

8. Kolmer, J. A.: Prevention of Non-Specific and Prezone Reactions in Wassermann Test with Sera and Spinal Fluids by Addition of Egg Albumin to Complement, Am. J. Clin. Path. **11**:402-413, 1941.

9. Kahn, R. L.: Optimal Zone Reaction in the Diagnosis and Treatment of Syphilis, Arch. Dermat. & Syph. **53**:633-642 (June) 1946.

10. Beerman, H.: Biologic False Positive Reactions to the Tests for Syphilis, Am. J. M. Sc. **209**:525-542, 1945; **210**:524-548, 1945.

dispose to false positive reactions. Stokes and his co-workers [11] considered the problem recently, Taussig [12] reported on it, as did Kolmer [13] and Rein and Elsberg.[14] Mohr, Moore and Eagle [15] early observed the occurrence of biologic false positive reactions in specimens of blood from clinically normal persons and nonspecific positive reactions in specimens of blood from patients with other organic diseases.[16]

Fortunately, these anomalous types of blood are not so frequent that the difficulties of diagnosis fail to yield eventually to a combination of a comprehensive clinical picture and repeated serologic testing. Kahn [17] worked extensively with his verification procedures, the aim being to differentiate between true syphilitic and biologic type positive reactions. Rein and Elsberg [18] described a verification test and attempted to evaluate current verification procedures. It would seem that major criticisms of verification procedures, criticisms arising from various investigations, stem from the fact that too much has been asked of the verification method. It was intended originally for use in relation to latent syphilis and not as the perfect test which would end all clinical perturbation.[18a]

Classic conditions which produce reactions simulating those of syphilis in laboratory studies are yaws, pinta, infections of the upper part of the respiratory tract, malaria, leprosy, tuberculosis and infectious mononucleosis. Ingestion of foods laden with fats, high protein intake and overindulgence in alcohol have been accused of producing seemingly valid yet nonspecific reactions with one or another serodiagnostic method.

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11. Stokes, J. H.; Boerner, F.; Hitchens, A. P., and Nemser, S.: Non-Specific Reactions in Routine Blood Testing for Syphilis, J.A.M.A. **130**:57-60 (Jan. 12) 1946.

12. Taussig, A. E.: On Persistence of Falsely Positive Serologic Tests for Syphilis in Non-Syphilitic Infections, J. Lab. & Clin. Med. **29**:473-477, 1944.

13. Kolmer, J. A.: Problems of Falsely Doubtful and Positive Reactions in Serology of Syphilis, Am. J. Pub. Health **34**:510-526, 1944.

14. Rein, C. R., and Elsberg, E. S.: Studies on Incidence and Nature of False Positive Reactions for Syphilis, Am. J. Clin. Path. **14**:461-469, 1944.

15. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: Occurrence in Normal Persons, Arch. Int. Med. **68**:898-912 (Nov.) 1941.

16. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: Occurrence with Organic Disease Other than Syphilis, Arch. Int. Med. **68**:1161-1178 (Dec.) 1941.

17. Kahn, R. L.: A New Verification Method in Serology of Syphilis, Univ. Hosp. Bull., Ann Arbor **8**:45-46, 1942; A Serologic Verification Test in the Diagnosis of Latent Syphilis, Arch. Dermat. & Syph. **41**:817-830 (May) 1940; Verification Test in Serology of Syphilis, J. Lab. & Clin. Med. **28**:1175-1186, 1943.

18. Rein, C. R., and Elsberg, E. S.: Are Current Verification Tests of Practical Value? J. Invest. Dermat. **6**:113-127, 1945.

18a. Since this paper was submitted for publication, the exhaustive studies made by Neurath and his co-workers (Am. J. Syph., Gonor. & Ven. Dis. **31**:347 [July] 1947) have shed new light on the problem of biologic false positive reactions.

Incitants of immune reactions, especially vaccinations against smallpox, have been implicated as productive of biologic false positive reactions. Cardon and Atlas [19] suggested that many types of hyperproteinemia may be responsible for nonspecific reactions.

What, then, is the answer? Until the perfect test is instituted, one which will unerringly choose the true and reject the false, the secret is unceasing vigilance on the part of both physicians and serologists. Pangborn [20] pioneered in the production of cardiolipin, a serologically active phospholipid, which gives promise of an accurately reproducible antigen and is usable for both complement fixation and flocculation procedures. This may solve, in the near future, the problem of serologic discord. Meanwhile, refusal on the part of physicians to accept any single performance test as the last word, careful checking of discrepancies by serologists by repeat procedures and the discriminating use of verification and quantitative tests can make the muddled picture of serologic conflict clearer. When the report of laboratory studies is sacred to serologists and a clue, rather than the voice of the oracle, to physicians, the discrepancies in serum diagnosis can become a help rather than a hindrance.

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19. Cardon, L., and Atlas, D. H.: Biologic False Positive Reactions for Syphilis Associated with Hyperproteinemia: Preliminary Report, Arch. Dermat. & Syph. **46**:713-720 (Nov.) 1942.

20. Pangborn, M. C.: Isolation and Purification of a Serologically Active Phospholipid from Beef Heart, J. Biol. Chem. **143**:247-256, 1942; A Simplified Preparation of Cardiolipin, with a Note on Purification of Lecithin for Serologic Use, ibid. **161**:71-82, 1945.

BIOLOGIC BASIS OF PSYCHOSOMATIC DISEASE OF THE SKIN

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IN RECENT years there has been a good deal of debate as to the importance of psychosomatic relations in cutaneous disease processes. Among the reasons for rejection by many dermatologists of the psychosomatic disease concept has been the fact that explanations of its mechanisms are usually couched in unfamiliar psychiatric terminology, while the possible underlying physiologic backgrounds are given relatively little attention. Possibly, a restatement in biologic terms may contribute to better understanding and wider acceptance of the theory. The objectives of psychosomatic medicine are "to study in their interrelation the psychologic and physiologic aspects of all normal and abnormal bodily functions, and thus to integrate somatic therapy and psychotherapy." [1] Certain principles of the cause of disease are implicit in this statement of aims. (1) A person reacts to environmental changes (chemical, physical, bacteriologic or psychologic) as a biologic entity, with concomitant responses in both psychic and somatic spheres. (2) Disease consists in alteration of the function of body organs as a response to these environmental changes. (3) The cause of disease resides then both in the person and in the particular environmental change encountered. When the so-called psychologic stimuli are considered further, certain facts become apparent: first, that all environmental changes affecting a person have psychologic accompaniments or repercussions; second, that the stimuli which produce reactions associated with maximal functional alterations are those of emotional nature, e. g., having to do with basic instinctual drives, such as self preservation and sexuality, and third, that the physiologic (somatic) component of the reaction is mediated by the autonomic nervous system. A brief review of the autonomic nervous system, its mode of action in emotions and the manner in which cutaneous reactions are effected may therefore be in order.

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1. Introductory Statement, Psychosom. Med. **1**:3 (Jan.) 1939.

The autonomic nervous system innervates involuntary muscle and glands. By means of its regulatory effects on these structures it maintains the constancy of internal bodily environment (homeostasis), while making adjustments for necessary somatic responses of the body to external environmental changes. Two divisions of the system are generally recognized: the sympathetic (thoracolumbar) and the parasympathetic (craniosacral), the higher centers for both being in the hypothalamus, which in turn has physiologic connections with the cortex and thalamus. The two divisions often exert opposing actions on the structures which they innervate in common, although in many instances a synergistic effect is demonstrable. It has been shown that the parasympathetic fibers are cholinergic; e. g., the effects on tissue are mediated by acetylcholine liberated at their terminals. Sympathetic fibers are generally adrenergic, liberating an epinephrine-like substance (sympathin) at their nerve endings. Autonomic fibers to sweat glands constitute the only exception, being functionally cholinergic although belonging to the sympathetic system. In response to certain stimuli massive responses of the autonomic system occur, designed for the total mobilization of the body's resources for some particular goal. Characteristic of such stimuli is that directly or indirectly they set into motion basic reflex reaction patterns having to do with fear, rage, sexual excitement and hunger, e. g., emotional responses. These responses are complex processes, with manifestations in the psychic, autonomic and somatic spheres. For example, an environmental stimulus eliciting the emotion of fear produces via the autonomic nervous system a series of physiologic changes, among which are peripheral vasoconstriction and splanchnic vasodilatation, increase in cardiac rate and output, heightened blood pressure, increased respiratory rate, increase in blood sugar, sweating, pilomotor activity, muscle tension and general interference with digestion and other anabolic processes. Concomitant psychic changes include the desire for flight, the awareness of danger, the consciousness of some of the concomitant visceral changes and an indescribable "affect" or feeling tone. A third and necessary part of the total response is the somatic activity appropriate to the situation—in this case, flight. In contrast to fear reactions, in which mainly sympathetic stimulation occurs, parasympathetic or vagotonic effects are prepotent in sexual excitement, while in rage there is an admixture of cholinergic and adrenergic effects. Ordinarily these signs of autonomic stimulation are transient, disappearing when effective somatic activity has caused the necessary adjustment in the external environment. For example, rage wanes when the infuriating cause has been appropriately dealt with; sexual excitement disappears with consummation of the sex act. However, when the normal somatic response is inhibited, or when the proper response cannot be selected because of conflicting stimuli, the physiologic "set" tends to persist for longer periods. Following repeated frustration of satsfaction of such

basic instinctual drives, chronic disorganization of vegetative functions may result. In this persistent overactivity of the autonomic nervous system which accompanies inhibition of somatic responses lies the physiologic basis for certain disorders in various organic systems, including the skin. There is ample experimental substantiation of this relationship. Masserman,[2] for example, trained cats to lift the lid of a box to obtain food when certain sensory stimuli were given. If after conditioning had been established an unpleasant inhibitory stimulus was administered (by blowing a disturbing air blast across the box) at the moment of food taking, certain persistent abnormalities in behavior developed. After only a few such experiences the animals showed manifestations of anxiety, "phobic" reactions to feeding signals, numerous psychologic abnormalities and refusal of food, along with persistent physiologic phenomena of the alarm state.

Gantt [3] observed that neuroses could be produced in dogs by severe emotional shocks, such as situations involving extreme fear, unusual scenes, prolonged and fierce fights and explosions. Among the artificial methods of producing experimental neuroses were the following: (1) setting up of a conflict between emotions or between two basic reflexes, such as the reactions to food and pain; (2) by a conflict between opposing stimuli, when differentiation was too difficult for the animal or positive and negative conditioned stimuli were applied simultaneously and (3) frustration of a conditioned response through failure to follow the signal with the expected satisfaction of the basic unconditioned reflex (for example, failure to provide the food which the animal had been trained to expect after hearing the sound of the bell). The symptoms of the resulting "neurosis" fell into four general categories: (1) active attempts to escape, (2) passive defensive measures (immobility and various motor disturbances), (3) permanent dysfunctions in various organic systems, producing circulatory, respiratory and alimentary disorders, and (4) autonomic changes detectable by laboratory study. Certain animals seemed predisposed to neurotic behavior, and these manifestations developed with relative ease. Anderson, Parmenter and Liddell [4] observed that sheep in which experimental neuroses had been produced showed decided general overreaction to stimulation, extreme restlessness and rapid respirations. In addition, an apparently permanent disorder of the cardiac action developed, manifested by rapid and irregular pulse

2. Masserman, J. H.: Experimental Neuroses and Psychotherapy, Arch. Neurol. & Psychiat. **49**:43-48 (Jan.) 1939.

3. Gantt, W. H.: Experimental Basis for Neurotic Behavior: Origin and Development of Artificially Produced Disturbances of Behavior in Dogs, New York, Paul B. Hoeber, Inc., 1944, p. 14.

4. Anderson, O. D.; Parmenter, R., and Liddell, H. S.: Some Cardiovascular Manifestations of the Experimental Neurosis in Sheep, Psychosom. Med. **1**:93-100 (Jan.) 1939.

with considerable increase in rate following numerous stimuli of a nonspecific nature. These experimental neurosis-producing situations find their counterpart in the frustrations of basic drives incident to modern civilized life, while the disturbances in behavior and in autonomic function of the experimental animals correspond closely to those seen in human neuroses.

With this psychophysiologic background, the mechanism of production of "psychosomatic" disorders in the skin may be stated as follows:

1. Manifestations of autonomic nervous system stimulation constitute an integral part of emotional reactions. Under this heading belong such well known phenomena as pallor, flushing, changes in temperature of the skin and changes in the activity of sweat and sebaceous glands. Activation of the effector mechanism in each case depends on the transmission of impulses from diencephalic centers via cholinergic and adrenergic fibers of the autonomic nervous system, with liberation of acetylcholine and sympathin, respectively, at the nerve endings, exactly as is the case with responses to change in temperature, exercise and the like, in which emotions are not concerned. When somatic expression of the emotion is inhibited by one of several mechanisms, the autonomic hyperactivity continues and may become intensified.

2. With greatly prolonged, frequently recurring or intense autonomic responses (e. g., the situation in the neurotic person, or in the normal person under stress) "functional" changes may pass over into the "organic." For example, the local asphyxia in persons with Raynaud's disease may terminate in gangrene and ulceration if emotionally caused stimulation of adrenergic fibers causing vasoconstriction is adequate to produce the requisite degree of anoxia. Emotional stimulation of parasympathetic fibers to cutaneous capillaries may cause vasodilatation and increased permeability through acetylcholine liberation, with resultant whealing (emotional urticaria). Purpura may result if the increase in permeability is such as to allow formed elements of the blood to pass (? hysterical stigmas). Pointing to the role of acetylcholine in the production of dyshidrosis is the report of Goldman.[5] This author cited Tilbury Fox's original description of dyshidrosis. "In all the severer cases patients have been the subject of great nervous debility, and in some cases have been under the care of physicians for various anomalous nervous diseases—odd muscular affections. Some have been prostrated by mental anxiety or worry. They always perspire too freely, are speedily exhausted, and are often dyspeptic." Goldman was able to reproduce the eruption in a group of psychoneurotic persons subject to this disease, by injections of a cholinergic drug (acetyl-beta-methylcholine).

5. Goldman, L.: Some Autonomic Nervous System Reactions in Selected Cases of Cheiropompholyx, M. Bull. Univ. Cincinnati **8**:79-88 (Feb.) 1941.

"Functional" changes may transform into the organic by a different mechanism, as, for example, when prolonged hyperhidrosis produces maceration of the plantar skin.

3. A plausible physiologic basis exists for the well known clinical observation that emotional stimuli may lower the threshold for allergic cutaneous reactions. Acetylcholine liberated at the terminals of cholinergic nerves (as a part of the autonomic changes in emotion) may have a synergistic effect with histamine produced by the local union of antigen and antibody, resulting in a clinical allergic reaction when the histamine alone would have been inadequate. Deutsch and Nadell [6] have shown that electrophoresis of acetylbetamethylcholine into the skin may increase the whealing response to histamine, while adrenergic drugs tend to diminish the reaction. Rothman and Coon [7] reported studies suggesting that liberation of acetylcholine plays a part in the production of the triple response of the skin to stimulation. Acetylcholine was demonstrable in the tissue fluid obtained from histamine wheals and from pathologic cutaneous lesions (neurodermatitis) in individual cases. Abramson [8] reported the case of a 31 year old woman in whom urticaria developed following ocean bathing, and showed on testing whealing reactions to cold. Onset of the disease followed a period of emotional strain; the clinical symptoms and the positive reactions to the test disappeared when the psychic difficulty was resolved.

4. Certain autonomic effects may change the resistance of tissues to pathologic processes. For example, hyperhidrosis, by producing favorable local conditions for the growth of fungi, may cause exacerbation of previously latent fungous disease. Prolonged anoxia of a part resulting from vasoconstriction may predispose to bacterial invasion by affecting p_H and/or the concentration of metabolites and other factors having to do with tissue resistance.

5. Autonomic effects on the viscera may indirectly affect the skin. Diabetes mellitus, if not actually initiated by prolonged emotional stress, is certainly exacerbated by it.[9] The hyperglycemic effect of emotion in the normal person is well known and operates at least in part through mobilization of glycogen by means of epinephrine. By this mechanism, then, dermatoses associated with diabetes may be affected by emotional reactions. Cutaneous disease due to nutritional deficiencies may in

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6. Deutsch, F., and Nadell, R.: Autonomic Skin Test with Electrophoresis, J. Invest. Dermat. **5**:87-94 (April) 1942.

7. Rothman, S., and Coon, J. M.: Studies on Liberation of Acetylcholine in the Skin. J. Invest. Dermat. **3**:99-106 (April) 1940.

8. Abramson, H. A.: Origin of Whealing Response to Cold, Psychosom. Med. **8**:435-440 (Oct.) 1941.

9. Woodyatt, R. T.: Psychic and Emotional Factors in General Diagnosis and Treatment, J. A. M. A. **89**:1013-1014 (Sept. 24) 1927.

certain instances be on the basis of functional gastrointestinal disorders which produce diarrhea, diminished absorption of essential foodstuffs and, in many cases, diminished total caloric intake. Possibly the cutaneous manifestations of hyperthyroidism also belong in this group, since there is considerable clinical evidence that emotional factors are important in the causation of thyroid disease.

6. It must be admitted that not all "functional" cutaneous diseases are generated by disorders of the autonomic functions. For example, self-induced eruptions, whether consciously or subconsciously produced, represent somatic behavior disturbances rather than autonomic reactions, although these somatic responses have the same causative background of frustration of basic drives. Many instances of anogenital pruritus, apparently related to the effects of repression in the sexual sphere, thus far are explainable only by reference to psychiatric concepts.

CONCLUSION

As a result of the autonomic stimulation attending emotional reactions, certain changes in the circulation and glandular activity of the skin become manifest. These changes are especially intense and prolonged when frustration of emotional satisfactions has produced chronic physiologic and behavior maladjustments (neurosis). Present day concepts of the chemical mediation of nerve impulses supply plausible mechanisms for the production in these circumstances of some instances of urticaria, persistent erythema (as rosacea), Raynaud's phenomenon and the like and for the exacerbation or precipitation of bacterial, fungous, metabolic and allergic diseases of the skin. Certain implications as to treatment may be drawn. Rational treatment of a neurotic patient with dermatologic manifestations should include measures directed at the source of the patient's illness—his emotional conflicts. It is difficult to see how any permanent benefit can accrue from such nonspecific measures as enforced rest, ultraviolet irradiation and heavy sedation. This form of treatment has long since been discarded in the management of patients with other physiologic manifestations of neurosis, and there is little reason to believe that patients with dermatologic disease will react favorably to it when the other types are unaffected. Instead, dermatologists, having recognized the nature of "functional" disorders, must learn to evaluate patients from the standpoint of the advisability and the necessity of psychiatric redirection. When there is sufficient time and insight and only superficial psychotherapy is needed, dermatologists may well serve as therapists, adding this modality to the rest of the therapeutic armamentarium. As always, patients with grave personality defects and deep-seated conflicts require referral to the psychiatrist.

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LEUKODERMA ACQUISITUM CENTRIFUGUM

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IN 1916 Sutton [1] called attention to a leukopigmentary anomaly which he named leukoderma acquisitum centrifugum. Hyde [2] is credited by Sutton in his textbook with first recognizing the disease when he presented a case before the Chicago Dermatologic Society in 1906 under the title "Vitiligo With a Central Mole." However, Hebra and Kaposi [3] mentioned the phenomenon in their textbook as early as 1874. In a general discussion of vitiligo they spoke casually of vitiligo that formed around preexisting nevi, and they cited other authors as to the causal role of injury, pressure, burns and constitutional disease in depigmentations. In 1910 Rolleston [4] noted and recorded the anomaly in a patient who was suffering from abdominal carcinomatosis. This patient was jaundiced, and the vitiliginous area surrounding the nevus was observed to take the yellow discoloration. In 1915 Almkvist [5] described a case of this sort, but called the achromic area a nevus anemicus. Recently Kuske [6] discovered a startling and exact depiction of the same disease in multiple lesions on one of the demoniac figures in a painting of the "Temptation of St. Anthony" on the Isenheimer Altar in the museum at Colmar, Alsace. This painting was

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1. Sutton, R. L.: An Unusual Variety of Vitiligo (Leucoderma Acquisitum Centrifugum): Report of Two Cases, J. Cutan. Dis. **34**:797, 1916.

2. Hyde, J. N.: Vitiligo with a Central Mole, J. Cutan. Dis. **24**:54, 1906.

3. Hebra, F., and Kaposi, M.: On Diseases of the Skin, Including the Exanthemata, translated and edited by W. Tay, London, The New Sydenham Society, 1874, vol. 3, p. 180.

4. Rolleston, H. D.: Jaundice with Areas of Unpigmented Skin, Proc. Roy. Soc. Med. (Clin. Sect.) **3**:195, 1910.

5. Almkvist, J.: Fall von eigentümlichen Naevi, Dermat. Wchnschr. **60**:74, 1915.

6. Kuske, H.: Ueber Leukoderma acquisitum centrifugum (Sutton), Dermatologica **88**:282, 1943.

done in the sixteenth century by Grünewald. It is not known whether the insert of the leukopigmentary anomaly came from the artist's imagination or whether one of his models actually showed the odd appearance that struck the artist as properly illustrative of demonism.

Whatever the priority in uncovering the disease that now bears Sutton's name, several reports in quick succession after Sutton's report, by Shelmire,[7] Bunch [8] and Stokes,[9] immediately established that it is not excessively rare. In the foreign literature, reports have been made by Montpellier,[10] Petges,[11] Narducci,[12] von Leszcyński [13] and von Poor.[14] The last extensive review was done by Feldman and Lashinsky [15] in 1936. There are several other papers of which Weber's,[16] Crawford's [17] and Niles's [18] are listed in the tabulation as of special note.

Our interest in this subject was aroused by our encountering 2 cases in quick succession. On looking into the matter, we are convinced that needless nosologic complexity and some error have been promulgated in attempts to separate this disease as something more than an interesting variant of vitiligo. We propose, therefore, after recording and illustrating 2 more cases, to comment critically on the various theories advanced about it.

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7. Shelmire, J. B.: An Unusual Variety of Vitiligo (Leucoderma Acquisitum Centrifugum), J. Cutan. Dis. **35**:163, 1917.

8. Bunch, J. L.: White Spot Disease and Vitiligo, Brit. J. Dermat. **30**:203, 1918.

9. Stokes, J. H.: Leukoderma Acquisitum Centrifugum (Sutton), Arch. Dermat. & Syph. **7**:611 (May) 1923.

10. Montpellier, J.: Vitiligo à début périnaevique, Bull. Soc. franç. de dermat. et syph. **29**:84, 1922.

11. Petges, M.: Naevus achromique (ou vitiligo périnaevique), Bull. Soc. franç. de dermat. et syph. **28**:302, 1921.

12. Narducci, F.: Sul neo leucopigmentario e sulla vitiligine perinevica, Arch. ital. di dermat. **1**:271, 1925.

13. von Leszcyński, R.: Ueber Suttonsche Krankheit (Leucoderma Acquisitum Centrifugum), Dermat. Wchnschr. **82**:575, 1926.

14. von Poor, F.: Ueber Leucoderma acquisitum centrifugum (Sutton), Dermat. Wchnschr. **80**:401, 1925.

15. Feldman, S., and Lashinsky, I. M.: Halo Nevus: Leukoderma Centrifugum Acquisitum (Sutton); Leucopigmentary Nevus, Arch. Dermat. & Syph. **34**:590 (Oct.) 1936.

16. Weber, F. P.: A Law Regarding the Distribution of Depigmented (Leucodermic) Patches of Vitiligo, When They Are Superadded to Mole-Like Nevi, Brit. J. Child. Dis. **21**:202, 1924.

17. Crawford, S.: Leukoderma Centrifugum Acquisitum, Arch. Dermat. & Syph. **9**:394 (March) 1924.

18. Niles, H. D.: Leukoderma Acquisitum Centrifugum, Arch. Dermat. & Syph. **43**:357 (Feb.) 1941.

REPORT OF CASES

CASE 1.—S. S., a 20 year old enlisted man in the United States Navy, entered the hospital for a gastric complaint. On general physical examination several coin-sized round and oval white spots were noted on the back. Closer inspection revealed that five out of twelve obvious lesions bore a macule or papule of hyperpigmentation in the nearly exact center. The others were unadorned as far as could be seen with the naked eye or hand lens magnification. The border of depigmentation was regular in most instances, but in some places a slightly serpentine or fine gearlike outline was discernible. Further search showed a patch of leukotrichia of recent origin, several more suggestive early lesions with and

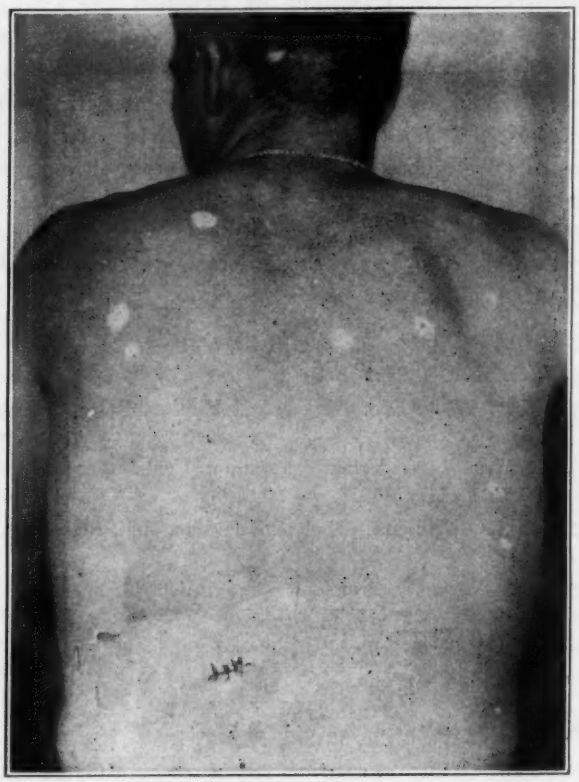

Fig. 1 (case 1).—Leukoderma acquisitum centrifugum, showing an area of leukotrichia.

without lentigines. In one place, in the posterior axillary line, there was an ordinary pea-sized nevus around which depigmentation was occurring. The impression here was as though the white halo was appearing under the gaze. In another site, on the thigh, depigmentation was in progress over a hematoma which resulted from recent trauma. The whole process began some three years earlier and was in active evolution. No lesion was known to have regressed.

CASE 2.—S. G., a private 19 year old patient of one of us (M. L.), was first seen for acne vulgaris. While under treatment, a solitary nevus, among many on the back, was discovered to be surrounded by a vitiliginous halo.

COMMENT

Before proceeding to specific comments, a word must be said about general theories of melanogenesis. Explanations of the exact chemistry of melanin and the physiology of pigment metabolism are still incomplete or in dispute. Whether dioxyphenylalanine is a naturally occurring propigment and whether there is a specific oxidase for it within

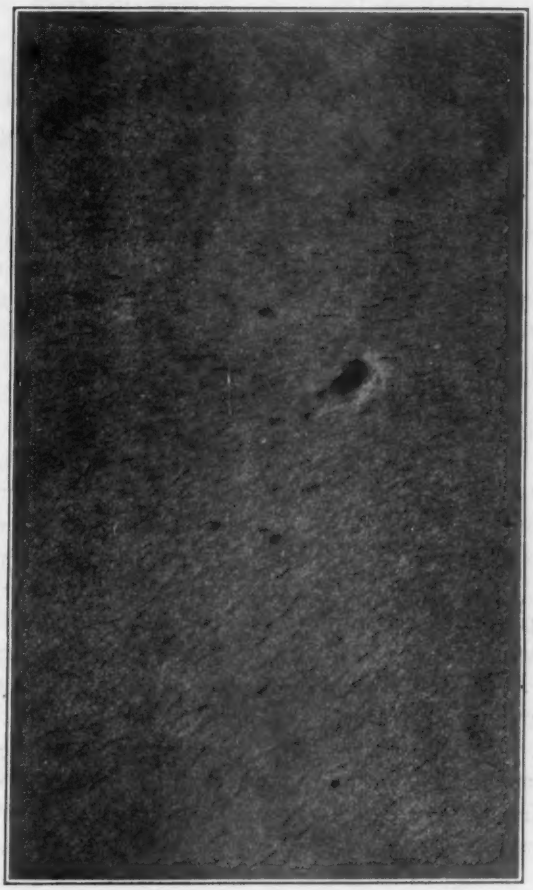

Fig. 2 (case 2).—Leukoderma acquisitum centrifugum.

melanoblasts, or whether tyrosine and tyrosinase are the ordinary substances involved or, finally, whether other amino acids or other chemical substances and their respective aminases or enzymes are essentially involved are questions yet to be settled. The origin, distribution and physiology of melanoblasts and melanophores constitute more problems to be elucidated. There is controversy about the basal cell theories

of Bloch and the neural cell theories of Masson. Consequently, the pathogenesis of pigmentary anomalies in directions either of increase or decrease is incompletely understood. However, the simultaneous appearance of both hyperpigmentation and depigmentation in an apparently causal anatomic relationship and in a striking geometric pattern has aroused special interest. That interest has led to theories about this leukopigmentary anomaly which range from simple identity with banal vitiligo to engaging, but in our opinion incorrect, ideas that it is an entity *sui generis,* nevoid in character. The pathogenesis of vitiligo is mysterious enough, and its resolution depends on the resolution of all the matters aforementioned. We think that nothing is gained and some misdirection is engendered by attempting to remove this leukopigmentary anomaly from clinical vitiligo.

Our next consideration is nomenclature. As a term, leukoderma acquisitum centrifugum describes a phenomenon of acquired progressive loss or displacement of pigment, or failure of pigment formation, from a centrum toward an expanding periphery. Clinically vitiligo seems to occur in precisely this manner, and therefore leukoderma acquisitum centrifugum is just as accurately descriptive of commonplace vitiligo. The term in itself does not suggest a mechanism, but if there is anything to the theory that Sutton's leukopigmentary anomaly is caused by a draining of pigment from the periphery toward concentration at the center, i. e., the opposite of vitiliginous progression, then the proper descriptive name should be leukoderma acquisitum centripetum. The idea of drainage of pigment is a common one and carries a specious attractiveness. One may pause for a moment to try to imagine what is meant by pigment being drained from one site to another. Is melanophoric transport meant? Does histologic evidence bear out such a supposition? Is there a hyperpigmented border around vitiligo, and if so, is it owing to physical displacement or transport of formed pigment? Or, is it due to more intense melanogenesis at the periphery? Or, is it all an optical illusion? Or, may pigment precursors be displaced centrifugally or centripetally and then either Sutton's phenomenon or plain vitiligo result? Or, finally, are all anomalies of pigmentation owing to physicochemical inhibition or stimulation in many patterns? In any event, if this disease is nothing more than vitiligo situated fortuitously around a preexisting nevus, and if a simple name is desired for the oddity, then some term like perinevic vitiligo (Narducci) or perinevic leukoderma is adequate. The virtue of these designations is that they do not prejudge causation in a disease and within a general situation in which causation is unresolved. On the other hand, halo nevus (Feldman-Lashinsky) and leukopigmentary nevus (Narducci) do prejudice the issue.

This brings us to consideration of theories that Sutton's leukopigmentary anomaly is a special type of nevus. Sutton originally, and Bunch subsequently, spoke of endothelial type cells composing the pigmented portion. This is now considered to have been a histologic mistake, and the cells in perinevic vitiligo are no more than ordinary

Summary of Some Previous Reports, with Theories, Notes or Comment

Author	Date	No. of Cases	Theory	Notes or Comment
Hebra and Kaposi [3]	1874	..	Vitiligo may form around preexisting nevi coincidentally	Vitiligo is caused by disturbances of innervation
Hyde [2]	1906	1	.....	"Vitiligo with a central mole"
Rolleston [4]	1910	1	.....	In a patient with carcinoma and jaundice
Almkvist [5]	1915	1	.....	The achromic area was taken to be nevus anemicus on clinical grounds
Sutton [1]	1916	2	.....	The vitiligo surrounded a nest of endothelial cells
Stokes [9]	1923	6	Leukoderma is caused by a physicochemical inhibition of melanogenesis	Similar appearances occur commonly around preexisting nevi, including the hairy variety, and around indisputably non-nevoid diseases, like psoriasis
Weber [16]	1924	1	Vitiligo, in general, tends to form around preexisting nevi	"Weber's law"
Crawford [17]	1924	1	.....	Noted hyperpigmentation around the vitiliginous portion, as in ordinary vitiligo
Narducci [12]	1925	2	.....	Proposed the designations; leukopigmentary nevus or perinevic vitiligo
von Leszczyński [13]	1936	1	.....	Vitiliginous halo varies directly in size with the size of the nevus
Feldman and Lashinsky [15]	1936	5	The whole disease is a nevus; the vitiliginous portion is nevus anemicus	Results of studies with heat, cold, histamine and other stimuli are claimed to be substantiating
Niles [18]	1941	Several	The vitiligo is caused by drainage of pigment to the center	Negative therapeutic results by destruction of center

nevus cells. The error, however, has tended to attract writers to make something more of the disease than vulgar vitiligo situated around a nevus. Thus, Feldman and Lashinsky, following Almkvist perhaps, suggest that perinevic vitiligo is not vitiligo at all but that the achromic area is nevus anemicus and the combination is a nevic entity. They bring to bear experimental evidence in the form of abnormal response of the vitiliginous portion to histamine, epinephrine, stroking, heat and irritation from mustard plaster. To us the experimental results

reported do not support the contention. Moreover, several authors[19] have reported similarly odd reactions in similar experiments on banal vitiligo.

It seems to us that there is an undue straining at the concept of nevus in this regard. In common parlance the word[20] is used in several senses. Ordinarily either a pigmented mole is indicated or a congenital anomaly of tissue is so referred to. Also the concept of tardive formation of nevi complicates the picture. It may be that some of the difficulty could be avoided if vitiligo itself could be considered a nevus in tardive form, and thus perinevic vitiligo could be conceived as nothing more than two common nevi in accidental or obligatory combination.

CONCLUSIONS

The likeliest conclusion is that vitiligo, perinevic vitiligo, leukoderma associated with syphilis, psoriasis, trauma, burns and the like have a common physicochemical mechanism of inhibition of pigment formation. The same in reverse may be said of anomalies of hyperpigmentation. And, short of ultimate resolution of the problem of melanogenesis, all that can be said at the moment is that phenomena like these accent the extreme lability of pigment formation and distribution.

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19. Goldsmith, W. N.: Recent Advances in Dermatology, Philadelphia, P. Blakiston's Son & Co., 1936, p. 61.

20. It may be of interest to note that students of language trace the word nevus to the Latin stem "gna" indicating nativity or birth. Some representative derived words are agnate, nation and nevus (cf. British spelling *naevus*).

CHEMISTRY OF PALMAR SWEAT

VI. Uric Acid

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PREVIOUSLY reported studies on the chemistry of palmar sweat from normal persons indicated that both chloride [1] and urea [2] were more concentrated in the so-called intermittent type of palmar sweat, when the gland was resting between secretions, than in the profuse type of palmar sweat, when the gland was secreting continuously (fig. 1 of the article by one of us [W. C. L.] and Osterberg on Urea [2]). Reducing substances (glucose),[3] on the other hand, seemed to meet an effective barrier in the palmar sweat secreting unit in both of these physiologic types of sweating, and only minimal amounts, if any, appeared in all palmar sweat even when the level of glucose in the blood was elevated acutely or chronically.

In order to obtain more information concerning the function of the normal individual sweat gland, these studies [4] were extended to include observations on the concentration of uric acid in palmar sweat. As in the previous studies, with the technic [5] used it was possible to collect pure uncontaminated sweat from the openings of individual sweat ducts and at the same time to observe the manner in which the sweat was secreted.

Previously reported studies [6] on the concentration of uric acid in sweat had been carried out on thermal-regulating sweat collected from

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1. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: II. Chloride, Arch. Dermat. & Syph. **56**:462-467 (Oct.) 1947.

2. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: IV. Urea, Arch. Dermat. & Syph. **56**:827-833 (Dec.) 1947.

3. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: III. Reducing Substances (Glucose), Arch. Dermat. & Syph. **56**:819-826 (Dec.) 1947.

4. Footnotes 1, 2 and 3.

5. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: I. Preliminary Report; Apparatus and Technics, J. Invest. Dermat. **6**:63-73 (Feb.) 1945.

6. (*a*) Plaggemeyer, H. W., and Marshall, E. K., Jr.: A Comparison of the Excretory Power of the Skin with that of the Kidney Through a Study of Human Sweat, Arch. Int. Med. **13**:159-168 (Jan.) 1914. (*b*) Barney, R. E.:

(Footnote continued on next page)

the general body surface. Values for uric acid reported in these studies ranged from zero to 1.7 mg. per hundred cubic centimeters of sweat. Adler [6j] was able to raise the level of uric acid in the sweat to as high as 30 mg. per hundred cubic centimeters by placing the subject on a diet rich in nucleoproteins. All investigators who have measured the concentration of uric acid in blood and sweat agreed that the concentration of this substance in the sweat is lower than in blood.

It is repeated again for emphasis that sweat which has been allowed to run off or is scraped off the body surface or absorbed into clothing is contaminated by epithelial cells, fat, oils, surface bacteria and so forth. This factor, together with the variety of technics used for the determination of uric acid, may well account for the differences in values already noted. The specificity of even the improved methods now available leaves much to be desired. It is therefore difficult to evaluate the results of studies which employed various methods for determination of uric acid in possibly contaminated sweat.

In the present study uric acid in palmar sweat was determined by the capillary tube colorimetric method of Bordley and Richards [7] (ultramicroadaptation of Folin's method), recently adapted by one of us

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Chemical Analysis of Sweat: A Preliminary Study, J.A.M.A. **85**:1373-1376 (Oct. 31) 1925. (*e*) Voit, K.: Untersuchungen über das Vorkommen von Harnsäure im menschlichen Schweiss, Arch. f. exper. Path. u. Pharmakol. **116**: 321-333, 1926. (*d*) Saiki, A. K., cited by Silvers, S.; Forster, W., and Talbert, G. A.: Simultaneous Study of the Constituents of the Sweat, Urine and Blood, also Gastric Acidity and Other Manifestations Resulting from Sweating: VI. Sugar, Am. J. Physiol. **84**:577-582 (April) 1928. (*e*) Saiki, A. K.; Olmanson, G., and Talbert, G. A.: Simultaneous Study of the Constituents of the Sweat, Urine and Blood, also Gastric Acidity and Other Manifestations Resulting from Sweating: IX. Uric Acid and Lactic Acids, ibid. **100**:328-330 (April) 1932. (*f*) Mosher, H. H.: Simultaneous Study of Constituents of Urine and Perspiration, J. Biol. Chem. **99**:781-790 (Feb.) 1933. (*g*) Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Role of Sweat as a Fungicide, with Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections, Arch. Dermat. & Syph. **39**:126-146 (Jan.) 1939. (*h*) Williams, J. W.: The Pathological Physiology of the Kidneys (and Sweat Glands) in Infections, Urol. & Cutan. Rev. **44**:47-49 (Jan.) 1940. (*i*) Mickelsen, O., and Keys, A.: The Composition of Sweat, with Special Reference to the Vitamins, J. Biol. Chem. **149**: 479-490 (Aug.) 1943. (*j*) Adler, A. E.: Ueber das Vorkommen von Harnsäure im Schweisse bei Gesunden und Kranken, Deutsches Arch. f. klin. Med. **119**: 548-560 (June) 1916.

7. Bordley, J., III, and Richards, A. N.: Quantitative Studies of the Composition of Glomerular Urine: VIII. The Concentration of Uric Acid in Glomerular Urine of Snakes and Frogs, Determined by an Ultramicroadaptation of Folin's Method, J. Biol. Chem. **101**:193-221 (June) 1933.

(W. C. L.) and Osterberg [8] to the spectrophotometer. The spectrophotometer was standardized for each analysis with a known standard solution of uric acid made fresh daily. The error for this method was plus or minus 0.1 mg. of uric acid per hundred cubic centimeters of sweat. The concentrations of uric acid in the blood were measured by Folin's direct method.[9]

Five normal men and 5 normal women between the ages of 21 and 35 years were studied. From this group a total of thirty-four successful collections and analyses of palmar sweat were made (table 1).

TABLE 1.—*Uric Acid in Palmar Sweat and Blood of Normal Persons*

Subject	Age, Years	Sex	Date, 1946	Physiologic Type of Sweating	Uric Acid, Mg. per 100 Cc.	
					Palmar Sweat	Blood
R. C.	25	F	2/18	Profuse	0.0	2.1
				Profuse	0.0	...
			2/22	Profuse	0.0	2.0
				Profuse	0.0	...
			3/ 5	Profuse	0.0	2.9
				Profuse	0.0	...
H. T.	29	M	2/19	Intermittent	0.8	3.0
			2/20	Intermittent	0.6	2.9
			3/ 4	Intermittent	0.1	3.4
J. H.	31	M	2/21	Intermittent	1.0	3.1
			3/ 5	Intermittent	1.2	3.1
			3/ 6	Intermittent	1.3	3.8
P. M.	21	F	2/20	Profuse	0.0	2.5
				Profuse	0.0	...
			2/22	Intermittent	0.5	1.9
			2/25	Profuse	0.0	2.1
D. M.	23	F	2/20	Intermittent	0.7	2.7
			2/21	Intermittent	0.8	2.6
			2/27	Profuse	0.0	2.7
				Intermittent	0.7	...
E. W.	35	F	2/27	Intermittent	0.6	2.5
			3/ 6	Intermittent	0.7	2.6
			3/11	Intermittent	0.4	2.4
G. S.	28	M	2/19	Intermittent	0.8	2.6
			3/ 8	Intermittent	0.8	3.2
			3/11	Intermittent	1.7	3.0
G. N.	27	F	3/ 8	Profuse	0.0	2.4
			3/11	Intermittent	0.4	3.1
P. C.	34	M	3/ 5	Intermittent	1.2	3.4
			3/15	Intermittent	0.8	3.1
			3/18	Intermittent	1.2	3.3
W. W.	33	M	3/11	Intermittent	0.6	3.7
			3/15	Intermittent	1.0	3.3
			3/16	Intermittent	0.5	3.4

Eleven of the collections (from 4 women) were of the so-called profuse physiologic type of sweat, in which the sweat was appearing at the openings of the sweat ducts continuously (figure 1 of the article by one of us [W. C. L.] and Osterberg on urea [2]). Twenty-three of

8. Lobitz, W. C., Jr., and Osterberg, A. E.: Use of the Spectrophotometer in Capillary Tube Colorimetry for the Determination of Reducing Substances (Glucose), Chlorides, Ammonia Nitrogen, Uric Acid and Creatinine, J. Invest. Dermat. **7**:135-144 (June) 1946.

9. Folin, O.: Standardized Methods for the Determination of Uric Acid in Unlaked Blood and in Urine, J. Biol. Chem. **101**:111-125 (June) 1933.

the collections (from 4 women and 5 men) were of the so-called intermittent physiologic type of sweat, in which the sweat gland was apparently resting between bursts of secreted sweat droplets (figure). Because of the larger volume of sweat needed for these chemical determinations (in comparison with the previous studies on palmar sweat [10]), there was only one instance (subject D. M., February 27) in which we were able to obtain both physiologic types of palmar sweat separately from the same subject during a single half-hour period of collection. All sweat volumes (output per minute) were measured, but, as before, they had no consistent correlation with the chemical composition of the sweat. These values were therefore omitted from the tables.

No uric acid was measurable in any of the eleven samples of the profuse type of palmar sweat, or, rather, by including the error of our method these concentrations of uric acid were less than 0.1 mg. per hundred cubic centimeters. On the other hand, the twenty-three samples of the intermittent type of palmar sweat yielded a mean concentration of uric acid of 0.8 mg. per hundred cubic centimeters (minimum 0.1 and maximum 1.7 mg.).

All specimens of blood contained normal amounts of uric acid, and these amounts had no relation to the amount of uric acid in either type of palmar sweat.

In order to study the effect on the level of uric acid in palmar sweat of concentrations of uric acid in the blood above the normal level we injected intravenously a 10 per cent solution of lithium urate in an amount equivalent to 22 mg. of uric acid per kilogram of body weight (10 mg. per pound). The lithium urate was prepared freshly as described by Folin, Berglund and Derick,[11] Berglund and Frisk [12] and Brøchner-Mortensen,[13] and the uric acid used in preparing the lithium urate solution was recrystallized according to the directions of Folin.[14] Despite these reports [15] we observed the intravenous administration of such a solution to be not without hazards to the subject, and we advise that the solution of lithium urate be injected into the vein slowly over a period of at least one and a half hours.

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10. Footnotes 2 and 3.

11. Folin, O.; Berglund, H., and Derick, C.: Uric Acid Problem: Experimental Study on Animals and Man, Including Gouty Subjects, J. Biol. Chem. **60**:361-471 (June) 1924.

12. Berglund, H., and Frisk, A. R.: Uric Acid Elimination in Man, Acta med. Scandinav. **86**:232-267, 1935.

13. Brøchner-Mortensen, K.: Uric Acid in Blood and Urine, Acta med. Scandinav. (supp.) **84**:137 and 158, 1937.

14. Folin, O.: Laboratory Manual of Biological Chemistry, with Supplement, ed. 5, New York, D. Appleton-Century Company, Inc., 1934, pp. 299-301.

15. Footnotes 11, 12 and 13.

Two normal men and 2 normal women (table 2) were given the solution of lithium urate intravenously. In both physiologic types of sweat collected in this experiment the concentration of uric acid was elevated above the fasting level when the concentrations of uric acid in the blood were also elevated. However, despite this elevation of the concentration of uric acid, the palmar sweat gland seems even more reluctant to excrete uric acid than does the renal excreting unit. With the level of uric acid in the blood between 5 and 6.4 mg. per hundred cubic centimeters, the level of uric acid in the palmar sweat rose only to a maximum of 0.5 mg. per hundred cubic centimeters for the profuse type and 2.1 mg. for the intermittent type of palmar sweat.

TABLE 2.—*Uric Acid in Palmar Sweat and Blood Before (Fasting) and After the Intravenous Administration of Lithium Urate**

Subject	Age, Years	Sex	Physiologic Type of Sweating	Time after Injection of Lithium Urate, Minutes	Uric Acid, Mg. per 100 Cc.	
					Palmar Sweat	Blood
			Fasting Values			
J. H.	31	M	Intermittent	..	0.4	2.7
			After Intravenous Injection of Lithium Urate			
			Intermittent	5	1.1	5.4
			Profuse	60	0.5	5.3
			Fasting Values			
P. M.	21	F	Profuse	..	0.0	2.6
			After Intravenous Injection of Lithium Urate			
			Profuse	5	0.2	5.8
			Profuse	60	0.3	5.0
			Fasting Values			
D. M.	23	F	Intermittent	..	0.3	2.6
			After Intravenous Injection of Lithium Urate			
			Profuse	5	0.5	6.4
			Fasting Values			
W. B.	28	M	Intermittent	..	0.3	2.2
			After Intravenous Injection of Lithium Urate			
			Intermittent	5	2.1	5.6

* The amount injected was 10 mg. of uric acid as lithium urate (10 per cent solution) per pound of body weight (22 mg. per kilogram). This solution was given by slow intravenous drip over one and a half hours.

SUMMARY

Thirty-four specimens of normal palmar sweat collected for the study of uric acid were grouped into two physiologic types: (1) profuse and (2) intermittent.

The profuse type of palmar sweat did not contain any measurable uric acid; the intermittent type of palmar sweat, however, had a mean value for uric acid of 0.8 mg. per hundred cubic centimeters. This value was much less than that of the simultaneously collected blood.

In 4 subjects the levels of uric acid in the blood were raised by the intravenous injection of solutions of lithium urate. The levels of uric acid in simultaneously collected palmar sweat were also elevated in both physiologic types. These elevations, though significant, were not great.

Clinical Notes

LICHEN SCROFULOSUS

Its Development During Treatment with Calciferol for Lupus Vulgaris

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Successful treatment for lupus vulgaris with large doses of calciferol (vitamin D_2) was first reported by Charpy of France in 1943.[1] This investigator, speculating that the increase of lupus vulgaris in France during 1941 was related to nutritional deficiencies and recognizing the favorable response of lupus to cod liver oil and heliotherapy, concluded that large doses of vitamin D might be beneficial in this condition. Calciferol in propylene glycol was administered by mouth to a series of 27 patients. The schedule of treatment was 15 mg., or 600,000 international units, of calciferol once weekly for three months followed by the same dose every two weeks for the next three months. In addition, a high calcium intake was prescribed, either in the form of 1 to 2 liters of milk or 0.5 Gm. of calcium gluconate daily. All 27 patients were considered clinically cured at the end of three months. The disease in 7 patients cleared on internal treatment alone, and 20 required electrocoagulation in addition to internal treatment.

Independently from Charpy, Dowling and Thomas[2] in England began the treatment for lupus vulgaris with calciferol in 1943. They reported a series of 38 patients who were treated with large doses of calciferol without an accompanying large intake of calcium. Their dosage schedule varied with the patient's reaction, the largest dose which was employed being 150,000 international units daily. In patients in whom symptoms of intolerance developed, this was reduced to 100,000 units and in some to 50,000 units daily. Of 32 patients in whom it was considered possible to assess the effects of treatment 18 appeared to be "cured" of lupus, 9 showed decided improvement, and 5 showed only moderate improvement. Of the 38 patients treated, 8 showed symptoms of intolerance to calciferol. In all except 1 these symptoms were mild, consisting chiefly of nausea, anorexia and depression. One patient on beginning treatment with calciferol experienced decided congestion and exudation of his lupous lesions. In 3 of the 38 patients hypercalcemia developed (up to 12.6, 13.8 and 14.8 mg. per hundred cubic centimeters, respectively). These high serum levels were not associated with higher dosages of calciferol in comparison with others and were not accompanied by clinical symptoms of intolerance.

In October 1946 the treatment for lupus vulgaris according to the dosage schedule which was described by Dowling and Thomas[2] was begun at the University of Chicago Clinics. The product used was "drisdol," each capsule containing 50,000 international units of calciferol. A reaction that was not previously reported which occurred in 1 of the patients so treated is described in the following case report.

REPORT OF A CASE

M. K., a 58 year old housewife, experienced lupus vulgaris in 1933. When she was seen in the clinic for the first time in July 1945, multiple lesions involved

1. Charpy, J.: Ann. de dermat. et syph. **3**:331 and 340, 1943; **4**:110 and 331, 1944.

2. Dowling, G. B., and Thomas, E. W. P.: Brit. J. Dermat. **58**:45, 1946.

the right side of the face, the lower part of the front of the neck, the posterior wall of the chest, the left hip, the right breast and the mucosa of the nose. Biopsies of lesions from the skin and the nasal mucosa confirmed the diagnosis of lupus vulgaris. Inoculation of a guinea pig with biopsy tissue did not elicit a reaction.

From July 1946 to October the patient was treated with a salt-free diet and local and general irradiation with ultraviolet rays. Initially improvement was observed under this regimen, but later new spread was noted.

On October 25 treatment with 150,000 units of calciferol daily was started. By December 2, definite regression of the lupus lesions was noted. Serum calcium on this date was 12.4 mg. and serum phosphorus 4.4 mg. per hundred cubic centimeters. The patient was seen next on December 11, at which time she complained of feeling tired. This general feeling of illness had come on with the appearance of a new eruption consisting of groups of pinhead-sized, reddish brown, follicular papules on the anterior, lateral and posterior aspects

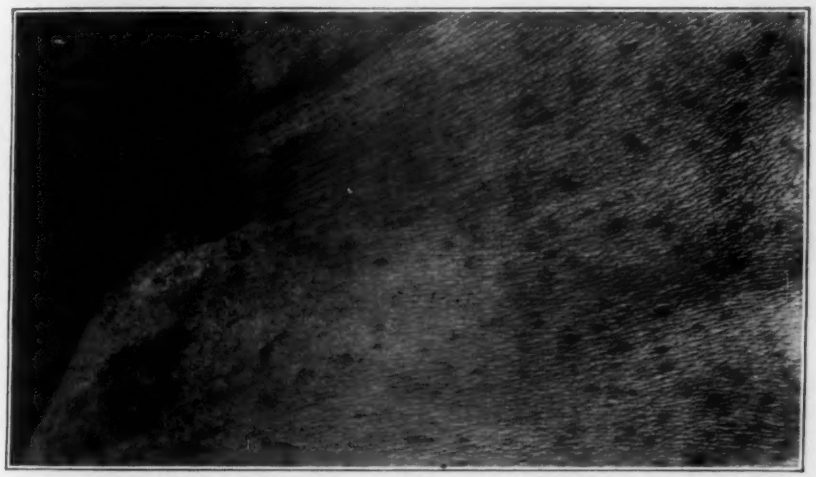

Fig. 1.—A close view of the eruption in lichen scrofulosus.

of the trunk. A close view of this eruption is shown in figure 1. The diagnosis of lichen scrofulosus was made. A biopsy of a lesion was made, and histologic sections later confirmed this diagnosis (fig. 2). The patient was ordered to discontinue the use of calciferol. She was next seen on December 18, at which time the sense of tiredness had progressed to a feeling of decided weakness. She also complained of frequency of urination, loss of appetite, nausea and vomiting. A particularly troublesome complaint was severe headache, which began in the occipital region, spread to involve the entire vertex and lasted from four to six hours. A loss of weight of 16 pounds (7.3 Kg.) had been noted since December 7.

The patient was admitted to Albert Merritt Billings Hospital on December 23. Physical examination did not reveal abnormalities except for the cutaneous lesions previously noted. A roentgenogram of the chest showed no evidence of active tuberculosis. Serum calcium was 13.6 mg. and serum phosphorus 4 mg. per hundred cubic centimeters. Results of other laboratory studies were within normal ranges. With treatment with bed rest and acetylsalicylic acid the patient rapidly became asymptomatic, and she was discharged from the hospital on December 30, at which time her calcium level was 12.8 mg. and phosphorus 2.2 mg.

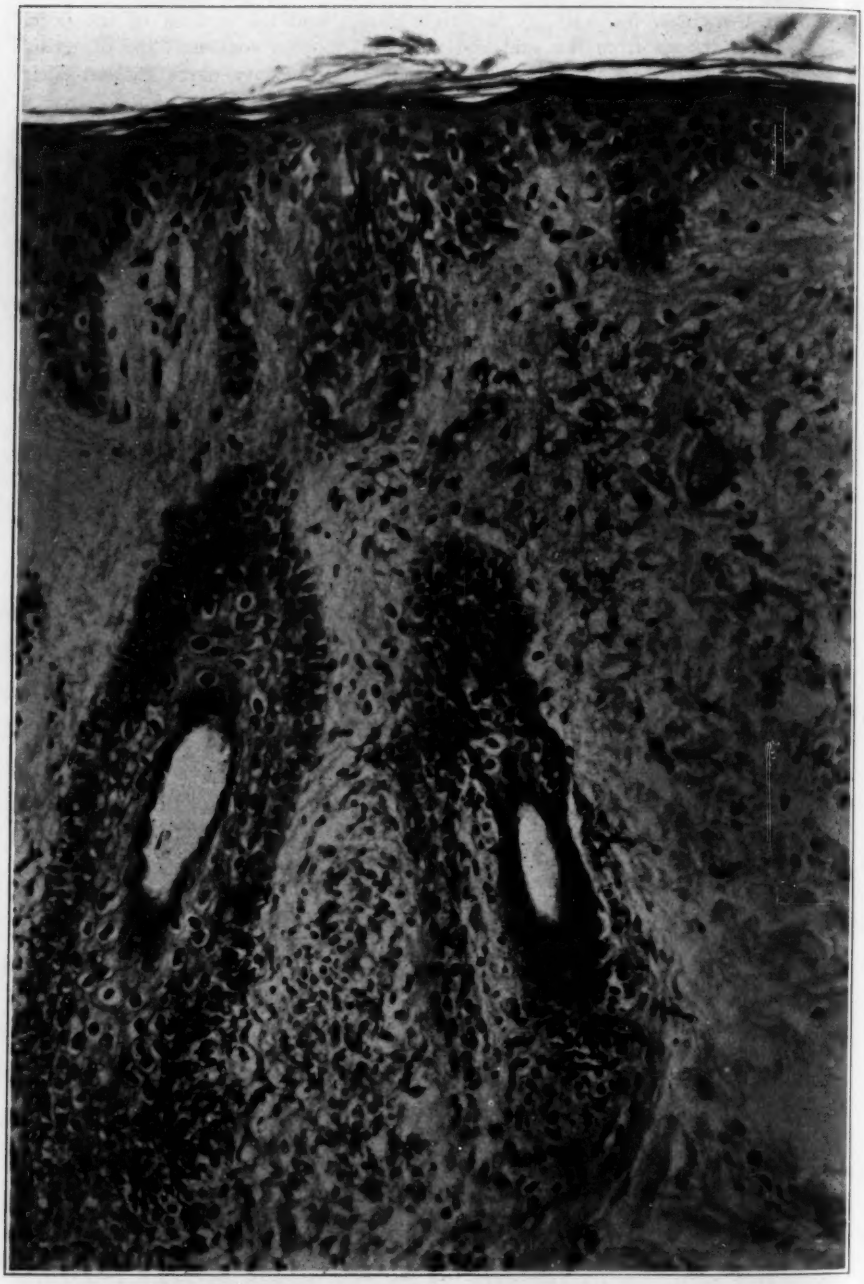

Fig. 2.—The section shows perifollicular infiltrates consisting of lymphocytes and epithelioid cells. A Langhans type giant cell is seen in the right upper corner.

per hundred cubic centimeters. Although calciferol was not taken after December 11, the lupus vulgaris lesions continued to regress. The lichen scrofulosus eruption faded relatively rapidly and by Jan. 15, 1947 was barely visible.

The toxicity of vitamin D preparations was thoroughly reviewed and interpreted by McLean [3] and by Steck and his colleagues.[4] The signs and symptoms exhibited by my patient correspond well with the description by these authors. However, so far it has been a unique experience to see the outbreak of a generalized tuberculid simultaneously with the development of vitamin D poisoning. It is remarkable that at about the same time rapid improvement of the lupus was noted.

The outbreak of tuberculids is often associated with rather sudden and rapid involution of tuberculous granulation tissue, for instance, in connection with focal reactions following injections of tuberculin or overdosage of heliotherapy. In my patient focal reactions as mentioned by Dowling and Thomas were not noted. Nevertheless, a rapid involution of lesions was unmistakably present. The development of lichen scrofulosus at that time strengthens the view that tuberculids develop when, in connection with rapid decomposition of tuberculous tissue, bacilli are mobilized, get into the blood stream and embolize in cutaneous capillaries. On reaching the skin the bacilli may be alive, dead or even broken into fragments. In persons with high tuberculin sensitivity, tuberculids will develop in response to cutaneous embolization of such fragments.

In any case, the appearance of a tuberculid at the height of poisoning from calciferol proves that the Charpy treatment has a powerful involuting effect on lupus infiltrates.

SUMMARY

A case of a patient with lupus vulgaris is described, who while undergoing treatment with calciferol experienced a cutaneous tuberculid along with signs and symptoms of calciferol intoxication. It is postulated that calciferol causes rapid decomposition of tuberculous tissue with possible hematogenous spread and embolization of tubercle bacilli or their products.

3. McLean, F. C.: Activated Sterols in Treatment of Parathyroid Insufficiency, J. A. M. A. **117**:606 (Aug. 23) 1941.

4. Steck, I. E.; Deutsch, H.; Reed, C. I., and Struck, H. C.: Ann. Int. Med. **10**:951 (Jan.) 1937.

PODOPHYLLUM THERAPY FOR PLANTAR WARTS

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The treatment of plantar warts has always been a difficult therapeutic problem. The almost invariable localization of such warts on the weight-bearing portions of the sole necessitates a form of treatment which will destroy the growth and at the same time permit active weight bearing on the treated area.

The number of methods of treatment advocated for this disease indicates that as yet there is no single completely satisfactory type of treatment. Surgical excision and curettage frequently prevent weight bearing for as long as three weeks. The possibility of a tender scar's resulting from such treatment must

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always be borne in mind. Trichloroacetic acid and other chemical mediums of destruction are slow, tedious and frequently followed by recurrence. Radiotherapy can be the method of choice only in the most experienced hands.

The report of Culp and Kaplan in 1944[1] on the treatment of condyloma acuminatum with podophyllum presented a new approach to this problem. A 25 per cent suspension of resin of podophyllum in liquid petrolatum was specifically curative when applied locally to acuminate warts. Clinical experience throughout the country has amply confirmed their claims. We attempted to use this preparation by surface application on plantar warts, and the results were disappointing.

Genital warts are in a state of constant maceration because of the sweating and friction that their location provides. This observation led us successfully to simulate such an environment for plantar warts by the direct application of adhesive tape over a treated lesion. Adhesive tape, acting as a seal to prevent evaporation, will cause the desired local maceration.

Our technic is as follows: The corneous upper layer of the wart is pared down until bleeding points are encountered. Pressure is then maintained with gauze until the bleeding stops. Paring the wart can be done quickly and painlessly with a small electric hand drill. A concavity is thus formed. The surrounding skin is painted for a distance of ½ inch (1.27 cm.) with collodion, and this is permitted to dry. The sole is held in a horizontal position, and a drop of the podophyllum suspension is placed into the excavation. A 2 inch (5.08 cm.) strip of well flamed adhesive tape is then placed directly over the lesion.

The patient is instructed to continue normal activity. It is important that the original tape be left intact. If it loosens, it may be resecured by application of successive layers of tape. By the third or fourth day, some tenderness may be noted. This usually lasts about twenty-four hours, and in our experience it has not been severe.

On the eighth day, when the tape is removed, the base of the wart can be seen as a gray friable substance, which can be scooped out. Podophyllum is reapplied and the above procedure repeated. Surrounding inflammation is minimal.

After the second or third treatment, a clean painless hole will be seen. This will heal rapidly, and in a few days healthy tissue will reach the surface.

The number of treatments that any wart may require can be determined only by experience. In our hands in the average successful response it has varied between three and four. One small wart was cured with a single application.

This treatment has been of great value in the mosaic type of wart, where the massive involvement excluded any other type of destructive treatment.

It may be expedient in certain cases which cannot be followed at weekly intervals to provide the patient with the podophyllum and collodion for home treatment, after careful instruction and demonstration of the method of application. A patient with a case of mosaic warts diffusely involving the anterior portions of both soles, which for three years was resistant to all forms of therapy, was cured with this type of home treatment.

In a relatively small series of cases we have cured 60 per cent of our patients. As our technic improves, we expect the percentage of cures to rise. A series of patients with verruca vulgaris on other parts of the body is being treated in the same way. Our results thus far indicate that such treatment is often effective.

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1. Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: Two Hundred Cases Treated wtih Podophyllin, Ann. Surg. **120**:251-256 (Aug.) 1944.

MOSAIC TYPE OF PLANTAR WART

Its Characteristics and Treatment

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The material in this paper formed the basis for an exhibit in the Scientific Section at the Fifth Annual Meeting of the American Academy of Dermatology and Syphilology, Cleveland, Dec. 8 to 12, 1946.

Since our paper [1] in 1937 interest in the mosaic wart has increased. MacKee,[2] Sutton [3] and others [4] have recognized it as a distinct and unusual type of plantar wart which is radioresistant and unresponsive to ordinary treatment for warts. However, it does respond to the chemosurgical therapy devised by us and by which we have cured 89.9 per cent of 109 patients of mosaic warts in private practice during the past five years. With this method there is no resultant scarring or injury to the fat pads, and the normal papillary linear arrangement returns. The patient remains ambulatory.

The mosaic wart has clinical characteristics which distinguish it from the single (traumatic) and mother-daughter (epidemic) types of plantar warts. The warty patch is horny and granular, with an irregular border, and varies in width from 1 mm. to 10 cm. Comparatively painless, the patch is located under the pressure points and may extend onto the toes and behind the heel. It is often mistaken for callus [5] and may be present for years.

Paring reveals the multicellular nature of the patch. Each consists of many small individual cores so closely grouped that they resemble a mosaic pattern. Even small satellite warts are multicellular. The cores vary from 1 to 3 mm. in diameter. Each has small capillaries perpendicular to the surface. Warts on the fingers more frequently accompany mosaic warts than ordinary plantar warts.

During the past five years, 109 patients with mosaic warts were treated in our private practice. Of these, 98, or 89.9 per cent, were cured and 11 not cured. The average age of the patients was 33.6 years, and the average duration was three years and seven months. Previous treatment had been given in a majority of the cases with roentgen rays, radium, acids and wart vaccines or with excision, electrosurgical intervention and intramuscular and local injections.

To effect a cure it was necessary to give the average patient eleven and two-tenths treatments, although this varied from two to thirty-three treatments. In patients not cured the average number of treatments was seven and two-tenths, which is less than that usually required.

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1. Montgomery, A. H., and Montgomery, R. M.: Mosaic Wart: An Unusual Type of Plantar Wart, New York State J. Med. **37**:1978 (Dec. 1) 1937.

2. MacKee, G. M., and Cipollaro, A. C.: X-Ray and Radium in the Treatment of Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1946, p. 503.

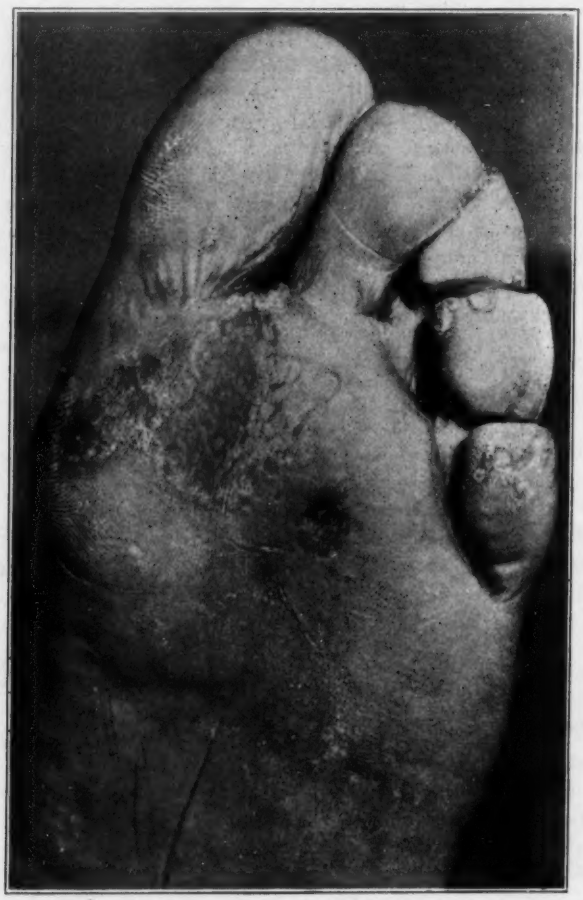
3. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939; reprinted, 1943, p. 857.

4. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 536. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 546.

5. Montgomery, R. M., and Montgomery, A. H.: Common Hyperkeratotic Lesions of the Foot, J. A. M. A. **124**:756 (March 18) 1944.

An outline of the chemosurgical method follows. Four chemical preparations are used: (*a*) silver nitrate solution: 1 Gm. to 1 cc. distilled water, (*b*) saturated solution of monochloroacetic acid, (*c*) 40 per cent salicylic acid plaster (Duke Laboratories) and (*d*) 60 per cent pulverized salicylic acid ointment-base white ointment U. S. P.

1. The area is pared until the capillary tips are visible or bleeding.
2. Capillary bleeding is stopped with silver nitrate solution.



Irregularly bordered patch, showing mosaic pattern with satellites nearby and on the toes.

3. The wart is swabbed lightly with saturated solution of monochloroacetic acid or silver nitrate solution.
4. Salicylic acid plaster, shaped to the size of the warty patch, is applied.
5. The same treatment is given to the satellites.
6. For more horny lesions the plaster is fortified with a thin coating of 60 per cent salicylic acid ointment.
7. For a deeper reaction saturated solution of monochloroacetic acid, instead of silver nitrate solution, is rubbed in.

8. The plaster is held in place with adhesive strapping.

9. The area is kept dry during treatment.

10. The lesion is pared down weekly to active warty tissue and the aforementioned steps are repeated.

11. When the area thins silver nitrate solution alone is used.

12. Every vestige of wart must be removed to prevent recurrence.

13. For severe reaction following the application of monochloroacetic acid the medication is removed, a wet dressing is applied and the tissue is pared down to release the subwart fluid.

14. Foam rubber pads, placed posterior to the wart, are used to relieve pressure.

15. Observation is continued for a month or two after apparent cure has been obtained.

SUMMARY

The clinical characteristics of the mosaic type of plantar wart are described.

An effective chemosurgical method is outlined.

Of 109 patients with mosaic warts 89.9 per cent were cured.

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STOMATITIS WITH GLOSSITIS FOLLOWING ORAL THERAPY WITH PENICILLIN TABLETS

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It has been shown that there is a potential buccal mucomembranous hypersensitivity in persons with contact dermatitis due to penicillin.[1] It has also been shown [1b] that topical use of penicillin in the mouth, especially with troches, can provoke stomatitis, both of the direct irritation type and the allergic contact type. The following cases of stomatitis, however, followed the administration of penicillin tablets. The patients improved rapidly when the antibiotic was discontinued, and the reactions were correlated with positive contact reactions of the buccal mucosa in tests with crystalline penicillin. With the relatively short period of contact with the buccal mucosa, it is surprising that such contact stomatitis reactions can occur.

REPORT OF CASES

CASE 1 (Stomatitis following prolonged oral therapy with penicillin tablets).—O. M., a 44 year old white woman, was first admitted to the Cincinnati General Hospital in 1934, with discoid lupus erythematosus.

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1. (*a*) Goldman, L.; Friend, F., and Mason, L. M.: Dermatitis from Penicillin, J. A. M. A. **131**:883 (July 13) 1946. (*b*) Goldman, L., and Farrington, J.: Contact Testing of the Buccal Mucous Membrane with Special Reference to Penicillin, Ann. Allergy **4**:457 (Nov.-Dec.) 1946.

Since that time she has had repeated admissions to the hospital with acute, subacute and even discoid disseminated phases. There was likewise an eruption from sulfonamide therapy in 1937. This patient was last admitted to the hospital on May 5, 1946, with an acute exacerbation and dissemination of typical lesions of lupus erythematosus on the face, shoulders, back and buttocks. There was a distinct palmar erythema covering both hypothenar eminences, and polyarthritis of the wrist and finger joints was noted. Oral penicillin therapy, with 100,000 units in tablets administered every three hours, was instituted May 22. The following levels of penicillin in the blood were obtained after the initial dose of 100,000 units of penicillin after the intervals listed.

15 min.	0.0
30 min.	0.0
1 hr.	0.4
2 hr.	0.0
3 hr.	0.0

The level in the urine after four hours was 0.5 per cubic centimeter. She was discharged from the hospital June 5, with the lesions of the skin the same, but the pain and swelling of the joints had receded. She continued oral penicillin therapy in dosage of 100,000 units every three hours, using in succession tablets of two commercial brands. There were no untoward reactions until after approximately three months, when the patient noted burning pain and tenderness of her tongue. Examination of the tongue and buccal mucosa showed them to be red and edematous. The tongue was tender to palpation, but there was no alteration of the papillae. Contact testing of the buccal mucosa with crystalline calcium penicillin G, the coloring matter and the coating of the tablets as controls resulted in a positive reaction with the penicillin and a negative reaction at the control test sites after twenty-four hours' contact time. Reactions to intradermal tests of the left forearm with 200 units of calcium penicillin G and patch tests on the arm were negative. These cutaneous tests were not repeated. Oral administration of penicillin was discontinued, and penicillin was given intramuscularly for several additional weeks, without any reactions. Approximately one year later the patient again received penicillin intramuscularly for an acute disseminate phase. There was no mucomembranous or cutaneous reaction.

Case 2 (Stomatitis after five days of oral penicillin therapy).—O. P., a 75 year old white man, when first seen at the Cincinnati General Hospital, was complaining of general malaise, headache and acute dermatitis of the left ear. Examination revealed an acutely, but not seriously, ill elderly white man with a sharply defined brawny dark red indurated shiny patch of acute dermatitis involving the left external ear and preauricular region of the face. His temperature was 100 F. A diagnosis of erysipelas was made. He was treated with 100,000 units of penicillin in tablets administered orally every three hours. Levels of penicillin in the blood were determined after the initial oral dose of 100,000 units of penicillin after the intervals listed:

15 min.	0.03
2 hr.	0.03
3 hr.	0.00

Two commercial brands of tablets were used in succession. On the third day, he was afebrile and most of the erysipelas had receded. Oral penicillin therapy, however, was continued in the same dosage. On the fifth day of treatment he complained of pain and tenderness of his tongue and throat. Examination revealed the buccal mucosa, tongue and anterior aspect of the pharynx to be red, moderately edematous and tender. The tongue and soft palate were covered with red papules,

but no pigmentation or alteration of the lingual papillae were noted. Perlèche-like fissures were noted at both labial commissures. He was thought to have contact penicillin stomatitis, and the ingestion of the tablets was discontinued. The stomatitis receded in forty-eight hours. One week later, contact testing of the buccal mucosa showed a positive reaction after one hour of contact time with the commercial tablets used. Control studies with all the other ingredients of the tablets, except penicillin, showed negative reactions of the oral mucous membrane in contact tests. Reactions to both an intradermal and a patch test of the left arm with crystalline sodium penicillin K were positive.

CONCLUSIONS

Two cases of stomatitis caused by penicillin orally administered for systemic diseases are reported. In 1 instance the disease was lupus erythematosus and in the other facial erysipelas. The clinical picture and reactions in controlled positive contact mucosal tests established the diagnosis. These cases furnish additional proof of the sensitizing character of penicillin.

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LAMB'S WOOL AS AN AID IN PREVENTING INFECTIONS OF THE EXTERNAL AUDITORY CANAL

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Infections of the external auditory canal, whether of mycotic or pyogenic origin, are notoriously prone to become chronic and rebellious to therapeutic measures. The use of lamb's wool in excluding water from the auditory canal is prevalent to some extent among swimmers and lifeguards.

During the war I served as dermatologist to a Marine Division in Guadalcanal, Okinawa, Guam and China. External otitis was widespread among the personnel in the tropics, and it was virtually impossible to persuade men to avoid swimming. In an attempt to keep the auditory canals reasonably dry, the patients were given a small supply of lamb's wool and instructed to roll up a tight little ball of the wool (about the size of a small marble) and gently force it into the auditory canal, being careful to avoid pushing it beyond the reach of the fingers. This plugging of the ears was advised at all times for swimming, showering and shampooing.

The results of this simple measure, when combined with the usual methods of local treatment, have usually been gratifying, not only in the tropics, where generally a dry skin is a healthy skin, but in temperate climates as well.

The little balls of wool can be used repeatedly until they become hardened. In my experience they are definitely superior to rubber plugs, and their use has proved to be a valuable adjunct in treating infections of the external auditory canal.

From the Pittsburgh Skin and Cancer Foundation.

Book Reviews

Handbook of Diagnosis and Treatment of Venereal Diseases. By A. E. W. McLachlan, M.D. Third edition. Price, $5. Pp. 384, with 160 illustrations (20 in color). Baltimore: Williams & Wilkins Company, 1947.

Concise and well illustrated, this volume, composed of twenty-one chapters, contains many useful charts and tables. There are 203 pages devoted to the diagnosis and treatment of the various types of syphilis and 108 pages to gonorrhea and its complications. Chancroid, nongonorrheal vulvovaginitis, urethroscopy and a group of diseases included under the heading "Other Conditions Commonly Referred to Venereal Disease Departments" are each considered in separate chapters. The paper, printing and illustrations are of fine quality.

As indicated by the author, this book was designed to provide ". . . an introduction to the principles of diagnosis and treatment of the venereal diseases, suitable . . . for the elementary student, yet adequate for the needs of the busy practitioner. . . ." The fact that it has gone through three editions since March 1944 is some indication of the demand for this type of text and the desire on the part of the author to keep it abreast of the new developments in a field that is changing in a kaleidoscopic manner.